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(71) Applicant *(for all designated States except US)*: GEORGETOWN UNIVERSITY [US/US]; Office of University Counsel, 37th and 0 Street N.W., Box 571246, Washington, DC 20057 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: KOZIKOWSKI, Alan, P. [US/US]; 12 Mershon Drive, Princeton, NJ 08540 (US). MA, Dawei [CN/US]; Georgetown University, 37th and 0 Street N.W., Box 571246, Washington, DC 20057 (US).

(74) Agent: VIKSNINS, Ann, S.; Schwegman, Lundberg, Woessner & Kluth, P.O. Box 2938, Minneapolis, MN 55402 (US).

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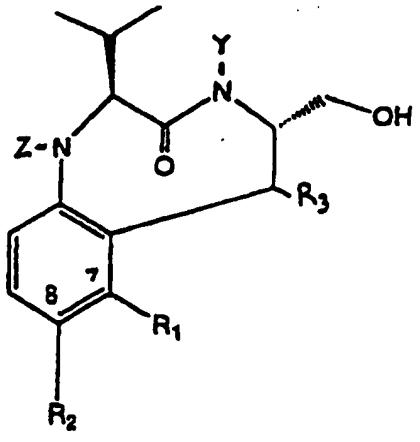
(54) Title: 8-HYDROCARBYL SUBSTITUTED BENZODIZOCINE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS PROTEIN KINASE C (=PKC) MODULATORS

(57) Abstract

Compounds of formula (I) wherein R_1 is H, (C_1-C_5)alkyl, OR^a, SR^a, $N(R^a)(R^b)$, halo, NO_2, $NHC(O)[(C_1$-$C_4)alkyl]$ or NHOH; R_2 is a (C_5-C_{22}) hydrocarbyl group, optionally comprising 1-3 double bonds, 1-2 triple bonds or a mixture thereof, or (C_6-C_{12})aryl(C_2-C_{10})alkyl, wherein the alkyl moiety optionally comprises 1-2 double bonds, 1-2 triple bonds or a mixture thereof; wherein said (C_5-C_{22}) hydrocarbyl group or said (C_6-C_{12})aryl(C_2-C_{10})alkyl may optionally be substituted with 1 or 2 substituents independently selected from the group consisting of halo, hydroxy, cyano, nitro, (C_1-C_5)alkyl, (C_1-C_5)alkoxy, trifluoromethyl, trifluoromethoxy, -C(=O)O(C_1-C_5)alkyl, and $N(R^e)(R^f)$; R_1 and R_2 together are $-CH(R^c)-CH_2-C(O)-N(R^d)-$, $-C(R^c)=CH-C(O)N(R^d)-$, $-C(R^c)=CH-N(R^d)-$ or $-C(R^c)=CH-O-$; R_3 is H, OH or halo; R^a and R^b are independently H or (C_1-C_5)alkyl; R^c is a (C_5-C_{22}) hydrocarbyl group; R^d is H or (C_1-C_5)alkyl; R^e and R^f are independently hydrogen, (C_1-C_5)alkyl, or (C_1-C_5)alkanoyl, or together with the nitrogen to which they are attached are pyrrolidino, piperidino or morpholino; Z is H or (C_1-C_5)alkyl, and Y is H or (C_1-C_5)alkyl; and their pharmaceutically acceptable salts, are PKC modulators and are useful for treating i.e. cancer mammals. Also disclosed are pharmaceutical compositions comprising compounds of formula (I), processes for preparing compounds of formula (I), and intermediates useful for preparing compounds of formula (I).



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8-HYDROCARBYL SUBSTITUTED BENZODIZOCINE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS PROTEIN KINASE C (=PKC) MODULATORS

Priority of Invention

This application claims priority from U.S. Provisional Application Number 60/017,532, filed May 10, 1996.

Background of the Invention

Protein kinases serve a regulatory function which is crucial for all aspects of cellular development, differentiation and transformation. One of the largest gene families of non-receptor serine-threonine protein kinases is protein kinase C (PKC). Since the discovery of PKC more than a decade ago by Nishizuka and coworkers (Kikkawa et al., J. Biol. Chem., 257, 13341 (1982)), and its identification as a major receptor for phorbol esters (Ashendel et al., Cancer Res., 43, 4333 (1983)), a multitude of physiological signaling mechanisms have been ascribed to this enzyme. The intense interest in PKC stems from its unique ability to be activated *in vitro* by diacylglycerol (and its phorbol ester mimetics), an effector whose formation is coupled to phospholipid turnover by the action of growth and differentiation factors.

The PKC gene family consists presently of 11 genes which are divided into four subgroups: 1) classical PKCα, β_1, β_2 (β_1 and β_2 are alternately spliced forms of the same gene) and γ, 2) novel PKCδ, ϵ, η, and θ, 3) atypical PKCζ, λ, η and ι and 4) PKCμ. PKCμ resembles the novel PKC isoforms but differs by having a putative transmembrane domain (reviewed in Blobe et al., Cancer Metast. Rev., 13, 411 (1994)); Hug et al., Biochem J., 291, 329 (1993); Kikkawa et al., Ann. Rev. Biochem, 58, 31 (1989)) (Figure 1). The α, β_1, β_2 and γ isoforms are Ca^{2+}, phospholipid- and diacylglycerol-dependent and represent the classical isoforms of PKC, whereas the other isoforms are activated by phospholipid and diacylglycerol but are not dependent on Ca^{2+}. All isoforms encompass 5 variable (V1-V5) regions and the α, β and γ isoforms contain four (C1-C4) structural domains which are highly conserved. All isoforms except PKCα, β, and γ lack the C2 domain, and the λ, η and ι isoforms also lack one of

two cysteine-rich zinc finger domains in C1 to which diacylglycerol binds. The C1 domain also contains the pseudo substrate sequence which is highly conserved among all isoforms, and which serves an autoregulatory function by blocking the substrate-binding site to produce an inactive conformation of the enzyme (House et al. Science, 238, 1726 (1987)).

Because of these structural features, diverse PKC isoforms are thought to have highly specialized roles in signal transduction in response to physiological stimuli (Nishizuka, Cancer, 10, 1892 (1989)), as well as in neoplastic transformation and differentiation (Glazer, Protein Kinase C, J. F. Kuo, ed., Oxford U. Press (1994) at pages 171-198).

From a pharmacological perspective, PKC has served as a focal point for the design of anticancer drugs (Gescher, Brit. J. Cancer, 66, 10 (1992)). Antisense expression of either the PKCα cDNA (Ahmad et al., Neurosurgery, 35, 904 (1994)) or a phosphorothioate oligodeoxynucleotide (S-oligo) for PKCα has shown the efficacy of targeting PKC to inhibit the proliferation of A549 lung carcinoma cells (Dean et al., J. Biol. Chem., 269, 16416 (1994)) and U-87 glioblastoma cells. Similar studies have not been conducted with breast tumors, but historical and preliminary data suggest that PKC is a logical molecular target by which to inhibit tumor growth and/or induce apoptosis. However, it is not clear which isoforms are most crucial for tumor proliferation and what role different PKC isoforms play in such critical cellular processes as cell proliferation and apoptosis. Nonetheless, it is reasonable to conclude that isoform selective, non-tumor promoting modulators of PKC that cause downregulation may find use in cancer treatment through the initiation of cancer cell death through apoptosis. Selective cancer cell killing may be achieved either through the targeting of those isoforms found to be overexpressed in the cancer cells, or through the synergistic interaction of a cytotoxic drug like 1-β-D-arabinofuranosylcytosine with an appropriate PKC-based signaling interceptor.

Teleocidin was first isolated from the mycelia of *Streptomyces mediocidicus* as a mixture of highly toxic compounds by Takahashi et al., Bull.

Agr. Chem. Soc. Japan, 24, 647 (1960). The structure of one of these metabolites was assigned by Hirata as shown by Figure 2, formula 1. The lyngbyatoxin series can be obtained together with the teleocidin B group from *Streptomyces mediocidicus* as disclosed by S. Sakai et al., Tetrahedron Lett., 27, 5219 (1986). Therefore, as depicted in Figure 2, they were named as teleocidin A-1 (**2a**) and A-2 (**2b**) by Sakai. Indolactam V (**3**, ILV), which contains the basic ring structure of the teleocidins, is the simplest member of the family, and is produced in large quantities by actinomycetes strain NA34-17 (Figure 2).

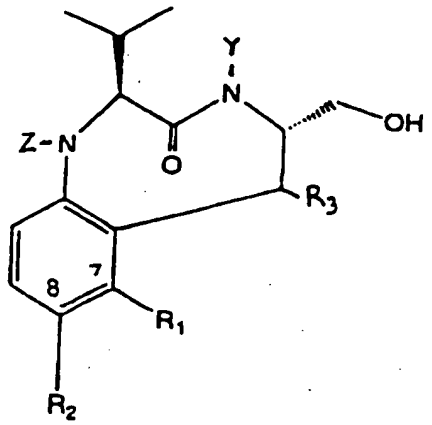
Investigations with 12-O-tetradecanoylphorbol-13-acetate (TPA) have provided considerable information on tumor promotion. In the two stage model of skin carcinogenesis, it is believed that initiators bind to DNA and that tumor promoters such as TPA bind non-covalently to membrane-associated high affinity receptors, most likely protein kinase C. Thus, TPA, the teleocidins, and the lyngbyatoxins as well as aplysiatoxin serve as diacylglycerol mimics, binding to the diacylglycerol site of protein kinase C, thus activating the kinase.

Indeed, computer assisted molecular modeling studies of these tumor promoters have revealed a commonality of their hydrophobic regions and certain heteroatoms. On the basis of both solution NMR studies and molecular mechanics calculations, it was additionally reported that the indolactam portion (indolactam V, **3**) of the teleocidins and lyngbyatoxins can exist in two conformational states, the sofa or twist-like conformations. At equilibrium, the ratio of twist/sofa was 2.8; the twist form of ILV represents the biologically active conformation.

Compounds related to the teleocidins are disclosed in Kozikowski, A. et al. Journal of the American Chemical Society, **1993**, 115, 3957-3965; in PCT Application WO/95-09,160 (1995); in Endo Y. et al. Journal of the American Chemical Society, **1996**, 118, 1841-1855; and in Endo Y. et al. Chem. Pharm. Bull. **1997**, 45, 424-426. However, a continuing need exists for novel compounds which can selectively modulate PKC so as to effect the selective killing of cancer cells.

Summary of the Invention

The present invention provides certain benzolactam PKC modulators, which exhibit PKC isoform selectivity. The compounds are of general formula (I):



(I)

wherein

R_1 is H, $(C_1$-$C_5)$alkyl, OR^a, SR^a, $N(R^a)(R^b)$, halo, NO_2, $NHC(O)[(C_1$-$C_4)$alkyl] or NHOH;

R_2 is a $(C_5$-$C_{22})$ hydrocarbyl group, optionally comprising 1-3 double bonds, 1-2 triple bonds or a mixture thereof, or $(C_6$-$C_{12})$aryl$(C_2$-$C_{10})$alkyl, wherein the alkyl moiety optionally comprises 1-2 double bonds, 1-2 triple bonds or a mixture thereof; wherein said $(C_5$-$C_{22})$ hydrocarbyl group or said $(C_6$-$C_{12})$aryl$(C_2$-$C_{10})$alkyl may optionally be substituted with 1 or 2 substituents independently selected from the group consisting of halo, hydroxy, cyano, nitro, $(C_1$-$C_5)$alkyl, $(C_1$-$C_5)$alkoxy, trifluoromethyl, trifluoromethoxy, $-C(=O)O(C_1$-$C_5)$alkyl, and $N(R^e)(R^f)$;

R_1 and R_2 together are $-CH(R^c)-CH_2-C(O)-N(R^d)-$, $-C(R^c)=CH-C(O)N(R^d)-$, $-C(R^c)=CH-N(R^d)-$ or $-C(R^c)=CH-O-$;

R_3 is H, OH or halo;

R^a and R^b are independently H or $(C_1$-$C_5)$alkyl;

R^c is a $(C_5$-$C_{22})$ hydrocarbyl group;

R^d is H or (C_1-C_5)alkyl;

R^e and R^f are independently hydrogen, (C_1-C_5)alkyl, or (C_1-C_5)alkanoyl, or together with the nitrogen to which they are attached are pyrrolidino, piperidino or morpholino;

Z is H or (C_1-C_5)alkyl; and

Y is H or (C_1-C_5)alkyl;

or a pharmaceutically acceptable salt thereof.

Pharmaceutical compositions comprising an amount of one or more compounds of formula (I) effective to treat mammalian conditions associated with pathological cellular proliferation, particularly human cancers, such as solid tumors and leukemias, are also an embodiment of the invention. The present invention also provides a method to inhibit the pathological proliferation of mammalian cells, such as cancer cells, by administering to a mammal afflicted with such a condition, an effective inhibitory amount of one or more of the compounds of formula I, preferably formulated as said pharmaceutical composition, i.e., in unit dosage form. Novel intermediates and processes to prepare compounds of formula (I), as depicted in Figures 6-12 are also embodiments of the invention.

The discovery of these new modulators of PKC that exhibit isotype selectivity will permit elucidation of the functional importance of the different PKC isoforms in the regulation of cell function, and can provide PKC based therapeutics that may find use not only in the treatment of cancer, but potentially autoimmune diseases, and inflammation.

Brief Description of the Figures

FIG. 1 shows the structural organization of the PKC gene family.

FIG. 2 shows the structures of telocidin B-4, A-1, A-2, and indolactam V.

FIG. 3 shows compounds of the invention.

FIG. 4 shows an electrophile useful for preparing compounds of the invention.

FIG. 5 shows an electrophile useful for preparing compounds of the invention.

FIG. 6 shows a scheme for preparing compounds of the invention.

FIG. 7 shows a scheme for preparing compounds of the invention.

FIG. 8 shows a scheme for preparing compounds of the invention.

FIG. 9 shows a scheme for preparing compounds of the invention.

FIG. 10 shows a scheme for preparing compounds of the invention.

FIG. 11 shows a scheme for preparing compounds of the invention.

FIG. 12 shows a scheme for preparing compounds of the invention.

FIG. 13 shows the cytotoxicity of compound **17** and ILV in MCF-7 and MDA-MB-231 breast carcinoma cells.

FIG. 14 shows the Western blot of PKC isoform levels 24 hours after treatment with compound **17**.

FIG. 15 shows the antitumor activity of compound **17** against the MDA-MB-231 xenograft in nude mice.

Detailed Description of the Invention

In the following description of the preferred embodiments, reference is made to the accompanying figures which form a part hereof, and in which is shown by way of illustration specific embodiments in which the invention may be practiced. It is to be understood that other embodiments may be utilized and structural changes may be made without departing from the scope of the present invention.

The following definitions are used, unless otherwise described. Halo is fluoro, chloro, bromo, or iodo. The term "alkyl" encompasses branched or unbranched alkyl, cycloalkyl or (cycloalkyl)alkyl, but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to. Aryl comprises a phenyl radical, an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic, as well as simple $(C_1\text{-}C_4)_n$ alkylaryl wherein n is 1-3.

It will be appreciated by those skilled in the art that compounds of the invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase).

Specific values listed below for radicals, substituents, and ranges, are for illustration only and they do not exclude other defined values or other values within defined ranges for the radicals and substituents

Specifically, $(C_1\text{-}C_5)$alkyl is methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, or cyclopentyl; and aryl is phenyl, methylphenyl, ethylphenyl, propylphenyl, dimethylphenyl, diethylphenyl, indenyl, methylindenyl, dimethylindenyl, naphthyl, methylnaphthyl, or dimethylnaphthyl.

A specific value for R_1 is OR^a, SR^a, $N(R^a)(R^b)$, halo, NO_2, $NHC(O)[(C_1\text{-}C_4)\text{alkyl}]$ or NHOH; for R_2 is 1-decynyl or decyl; for R_3 is H; for R^c is $(C_5\text{-}C_{15})$alkyl; for Y is H; and for Z is methyl.

A more specific value for R_1 is OR^a.

A specific group of compounds are compounds of formula I wherein R_1 and R_2 together are $-CH(R^c)-CH_2-C(O)-N(R^d)-$, $-C(R^c)=CH-C(O)N(R^d)-$, $-C(R^c)=CH-N(R^d)-$ or $-C(R^c)=CH-O-H$; or a pharmaceutically acceptable salt thereof.

Another specific group of compounds are compounds of formula I wherein Z is CH_3; Y is H; R_1 is OR^a, SR^a, $N(R^a)(R^b)$, halo, NO_2, $NHC(O)[(C_1\text{-}C_4)\text{alkyl}]$ or NHOH; R_2 is $(C_5\text{-}C_{15})$alkyl, optionally comprising 1-3 double bonds, 1-2 triple bonds or a mixture thereof; and R_3 is H; or a pharmaceutically acceptable salt thereof.

Another specific group of compounds are compounds of formula I wherein: R_1 is OR^a, SR^a, $N(R^a)(R^b)$, halo, NO_2, $NHC(O)[(C_1\text{-}C_4)alkyl]$ or NHOH; and R_2 is a hydrophobic $(C_5\text{-}C_{22})$ hydrocarbyl group, optionally comprising 1-3 double bonds, 1-2 triple bonds or a mixture thereof, or $(C_6\text{-}C_{12})aryl(C_2\text{-}C_{10})alkyl$, wherein the alkyl moiety optionally comprises 1-2 double bonds, 1-2 triple bonds or a mixture thereof; or R_1 and R_2 together are $-CH(R^c)\text{-}CH_2\text{-}C(O)\text{-}N(R^d)\text{-}$, $-C(R^c)=CH\text{-}C(O)N(R^d)\text{-}$, $-C(R^c)=CH\text{-}N(R^d)\text{-}$ or $-C(R^c)=CH\text{-}O\text{-}H$; or a pharmaceutically acceptable salt thereof.

Another specific group of compounds are compounds of formula I wherein: R_2 is $(C_5\text{-}C_{15})alkyl$, optionally comprising 1-3 double bonds, 1-2 triple bonds or a mixture thereof; or a pharmaceutically acceptable salt thereof.

Another specific group of compounds are compounds of formula I wherein: R_2 is $(C_6\text{-}C_{12})aryl(C_2\text{-}C_{10})alkyl$, wherein the alkyl moiety optionally comprises 1-2 double bonds, 1-2 triple bonds or a mixture thereof; or a pharmaceutically acceptable salt thereof.

A preferred group of compounds are compounds of formula I wherein Z is CH_3; Y is H; R_2 is $(C_5\text{-}C_{15})alkyl$, optionally comprising 1-3 double bonds, 1-2 triple bonds or a mixture thereof; and R_3 is H; or a pharmaceutically acceptable salt thereof.

Another preferred group of compounds are compounds of formula I wherein R_2 is 1-decynyl; or a pharmaceutically acceptable salt thereof.

Processes for preparing compounds of formula I are provided as further embodiments of the invention and are illustrated by the following procedures in which the meanings of the generic radicals are as given above unless otherwise qualified.

Compounds of formula I wherein R_1 is 1-alkynyl can be prepared from a corresponding compound wherein R_1 is iodide by coupling with the requisite alkyne using a suitable catalyst, such as for example palladium. Suitable conditions for such a coupling reaction are illustrated in Example 1.

Compounds of formula I wherein R_1 is 1-alkyl can be prepared from a corresponding compound wherein R_1 is 1-alkynyl by hydrogenation of

the alkyne bond using a suitable catalyst, such as for example palladium on carbon. Suitable conditions for such a hydrogenation are illustrated in Example 2.

Compounds of formula I can generally be prepared by the reaction of 2,6-disubstituted arylmetal compounds as nucleophiles with enantiomerically pure three carbon electrophiles incorporating the necessary amino and hydroxyl groups in protected form.

Electrophiles.

Two readily available electrophiles (Figures 4 and 5) are suitable for preparing compounds of the invention, the protected aziridinemethanol **21**, and the protected serine aldehyde **23** ("Enantiospecific Synthesis of D-α,ω-Diaminoalkanoic Acids" Beaulieu, P. L.; Schiller, P. W. *Tetrahedron Lett.* **1988**, *29*, 2019-2022). To obtain compound **21**, the known L-serine-derived methyl or benzyl esters **20** can be reduced to the aziridinemethanol, e. g., with $NaBH_4$ and the hydroxyl group silylated [(a) "Construction of Optically Pure Tryptophans from Serine Derived Aziridine-2-carboxylates" Sato, K.; Kozikowski, A. P. *Tetrahedron Lett.* **1989**, *31*, 4073-4076. (b) "One-Step Synthesis of Optically Active Benzyl N-Trityl-*L*-Aziridine-2-Carboxylic Esters" Kyul-Yeheskiely, E.; et al. *Tetrahedron Lett.* **1992**, *33*, 3013-3016] ("Derivatives of heterocyclic α-iminocarboxylic acids. 4. Reduction of N-alkoxycarbonyl derivatives of α-iminocarboxylic acids" Nurdinov, R.; et al. *Khim. Geterotsikl. Soedin.* **1993**, 1567-1573; *Chem. Abstr.* **1995**, *123*, 83337x). Since cuprates exhibit enhanced reactivity towards aziridines compared with organolithium reagents, stoichiometric or catalytic amounts of copper(I) salts may be included in reaction mixtures involving **21**.

Nucleophiles.

The most convenient nitrogen substituent on the aromatic ring would be a free amino group (NH_2). While, N-alkylarylamines have been

successfully ortho-metalated by N-lithiation, reacted with CO_2 to form the lithium carbamate, and further treated with *tert*-butyllithium, this procedure failed in the case of aniline ("Carbon Dioxide: A Reagent for the Simultaneous Protection of Nucleophilic Centers and the Activation of Alternative Locations to Electrophilic Attack. 17. Substitution of *N*-Methyl-1- and *N*-Methyl-2-naphthylamine and Side-Chain Functionalization of *o*-Toluidine" Katritzky, A. R.; et al. *J. Org. Chem.* **1991**, *56*, 5045-5048). *N*-(methoxycarbonyl)-*O*-(methoxymethyl)-*m*-aminophenol has been reported to undergo directed metalation mainly in the 2-position, whereas the corresponding N-Boc derivative reacted on the opposite side of the nitrogen in position 4 ("Biosynthesis of Sarubicin A. Synthesis and Incorporation of 6-Hydroxy[$^{13}CO^{15}NH_2$]anthranilamide" Gould, S. J.; Eisenberg, R. L. *J. Org. Chem.* **1991**, *56*, 6666-6671). Since the nitrogen may need to be deprotected in the presence of protecting groups such as N-Cbz and O-TBDMS, the N-(allyloxycarbonyl) derivative **24** (Figure 6) is a convenient starting material for preparing compounds of the invention. While the allyloxycarbonyl group is not bulky, it is readily removed by various nucleophiles or hydride donors in the presence of a Pd catalyst.

An intermediate of formula **28** is particularly useful for preparing compounds of formula I. An intermediate of formula **28** can be prepared as shown in Figure 6 by reaction of a nucleophile of formula **24** and an aziridine (electrophile) of formula **21** followed by deprotection of the aniline nitrogen. The resulting aniline **25** can be alkylated to give a compound of formula **26.** Hydrogenation of **26** followed by lactam formation yields an intermediate of formula **28.**

The methoxymethoxy substituent in intermediate **28** provides access not only to 7-hydroxy- and 7-alkoxybenzolactams but, as discussed below, to a variety of other compounds of the invention via aryl triflate chemistry.

Benzolactams containing 7-halo or 7-CF_3 substituents can conveniently be synthesized from the requsite *N*-(allyloxycarbonyl)-*m*-

substituted anilines using a procedure similar to the one described above. A variety of potentially suitable substrates have been reported which differ in their thermal stability as well as in the ease or difficulty with which the second substituent can be transformed into NH_2. 3-Chlorobenzonitrile and *N-tert*-butyl-3-chlorobenzamide undergo directed lithiation in position 2 at -70°C, and the resulting organolithiums can be trapped with an electrophile ("Heteroatom-Facilitated Lithiations" Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1-360 (unpublished results by Rodriguez, H. R.)). 3-Fluoro- and 3-chlorophenyloxazolines have been metalated in position 2 ("A New Route to 3-Hydroxyphthalides: Application to the Synthesis of Racemic [5-^{13}C] Daunomycinone" Becker, A. M.; et al. *Tetrahedron Lett.* **1986**, *27*, 3431-3434.) and ("The Oxazoline-Benzyne Route to 1,2,3-Trisubstituted Benzenes. Tandem Addition of Organolithiums and α-Lithionitriles to Benzynes" Pansegrau, P. D.; et al. *J. Am. Chem. Soc.* **1988**, *110*, 7178-7184). Additionally, 3-Fluorobenzaldehyde dimethyl acetal undergoes metalation and subsequent carboxylation in high yield ("Synthesis of Functionalized Hydroxyphthalides and Their Conversion to 3-Cyano-1(3*H*)-isobenzofuranones. The Diels-Alder Reaction of Methyl 4,4-Diethoxybutynoate and Cyclohexadienes" Freskos, J. N.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1985**, *50*, 805-810).

The 7-halo-6-hydroxybenzolactams of the invention can conveniently be prepared as illustrated in Figure 7. Lithiated 3-fluoro- and 3-chlorobenzaldehyde dimethyl acetal **35a,b** can be reacted with aldehyde **23**. Separation of the resulting stereoisomers followed by acid hydrolysis of the aryllithium addition product **36**, yields an aldehyde, which forms a hemiacetal with the benzylic hydroxyl group (**37**). Benzylic alcohol **37** can be selectively oxidized to a lactone using, for example, MnO_2. Acetonide protection can then be restored. The lactam can be ammonolyzed to yield **39**, and the liberated benzylic hydroxyl group protected by silylation. Hofmann degradation gives an aniline of formula **40**, which can be converted to the bis-*tert*-butyldimethylsilyl ether **41**. Using a sequence similar to that illustrated in Figure 6, a compound of formula **41** can be converted to a 7-halo-6-hydroxybenzolactam of formula **42**.

Compounds of the invention wherein R_3 is fluoro (such as for example a compound of formula **43** can be prepared by treatment of a corresponding compound wherein R_3 is hydroxy (such as for example a compound of formula **42**) with (diethylaminosulfur)trifluoride (DAST) as shown in Figure 7.

A compound of formula I wherein R_3 is hydrogen can be prepared from a corresponding compound of formula I wherein R_3 is hydroxy, such as for example a compound of formula **42** , by formation of a cyclic thionocarbonate of formula **44** followed by Barton deoxygenation ("Synthesis of Deoxysugars and Deoxynucleosides from Diol Thiocarbonates" Barton, D. H. R.; Subramanian, R. *J. Chem. Soc., Chem. Commun.* **1976**, 867-868).

As illustrated in Figure 8, the intermediate aryl triflate **46**, can be used to prepare compounds of formula I having a variety of 7-substituents. Methoxycarbonylation of **46** ("Palladium Catalysed Alkoxycarbonylation of Phenols to Benzoate Esters" Dolle, R. E.; et al. *J. Chem. Soc., Chem. Commun.* **1987**, 904-905) gives the ester **47** which can be transformed into the derivatives **48** and subsequently compounds of formula **49**, by selective reduction of the ester moiety, followed by cuprate alkylation of the derived triflate.

The ester function of a compound of formula **47** can also be used to introduce a nitrogen atom into position 7 by means of a Curtius degradation. The product **50** can be alkylated in position 8 as previously illustrated in Figure 6 to obtain compound **51**. This intermediate can be used to prepare 7-nitro- and 7-(hydroxyamino)benzolactams **53**, **54** by peracid oxidation and reduction with zinc.

Diazonium chemistry can be applied to **51** to prepare the 7-iodo- and 7-mercapto derivatives **55**, **56**. The corresponding chlorides and bromides may be obtained from **51** by action of *tert*-butyl nitrite and the anhydrous copper(II) halides ("Alkyl Nitrite-Metal Halide Deamination Reactions. 2. Substitutive Deamination of Arylamines by Alkyl Nitrites and Copper(II) Halides. A Direct and Remarkably Efficient Conversion of Arylamines to Aryl Halides" Doyle, M. P.; et al. *J. Org. Chem.* **1977**, *42*, 2426-2431). The

corresponding fluoride may be obtained from **51** using a procedure similar to that described in "A Mild and Efficient Method of Aromatic Fluorination" Rosenfeld, M. N.; Widdowson, D. A. *J. Chem. Soc., Chem. Commun.* **1979**, 914-916.

Compounds of formula I wherein R_1 and R_2 together are -$CH(R^c)$-CH_2-$C(O)$-$N(R^d)$-, -$C(R^c)$=CH-$C(O)N(R^d)$-, -$C(R^c)$=CH-$N(R^d)$- or -$C(R^c)$=CH-O- can be prepared using procedures similar to those illustrated in in Figure 9. Iodophenol **58** and the iodoaniline **59** can be alkylated with the allylic halide **60**, and the resulting intermediates cyclized under Pd catalysis to obtain the benzofuran **63** ("Synthesis of Benzofurans, Tetrahydrobenzopyrans, and Related Cyclic Ethers via Cyclic Carbopalladation" Negishi, E.; et al. *Heterocycles* **1989**, *28*, 55-58) and the indole **64** ("Conversion of 2-Halo-N-allylanilines to Indoles via Palladium(0) Oxidative Addition-Insertion Reactions" Odle, R.; et al. *J. Org. Chem.* **1980**, *45*, 2709-2710). An intermolecular Heck reaction between **59** and dimethyl maleate gives quinolinone **65** ("Palladium-Catalyzed Synthesis of 2-Quinolone Derivatives from 2-Iodoanilines" Cortese, N. A.; et al. *J. Org. Chem.* **1978**, *43*, 2952-2958). Elaboration of the methoxycarbonyl side chain in quinolinone **65** to an alkyl group, using standard conditions, yields the alkylated compound **66**. Hydrogenation of the unsaturated heterocyclic ring of compound **66** gives the lactam stereoisomers **67**.

An intermediate of formula **28** can alternatively be prepared as illustrated in Figure 10. 1,3-Cyclohexanedione **69** can be alkylated with aziridine **68** obtained by coupling the serine and valine building blocks. Removal of the N-protective group yields a compound which can close to the eight-membered lactam ring under conditions of enamine formation (high dilution), to give enaminone **73**. Aromatization of enaminone **73**, using standard conditions, gives compound **75**, which can be protected to give an intermediate of formula **28**.

Compounds of formula I can also be prepared using a sequence similar to that described in the previous paragraph. As shown in Figure 10,

alkylation of the dianion of **69** gives the substituted cyclohexanedione **70**. Subsequent alkylation with the aziridine **68**, followed by N-deprotection gives the cyclic enaminone **74**, which can be elaborated to compounds of formula **76** and **33**.

Compounds of formula I wherein R_1 is H can generally be prepared using procedures similar to those described in Examples 1 and 2, as illustrated in Figure 11.

Compounds of formula I wherein R_1 is OR^a can generally be prepared using procedures similar to that described in Example 3, as illustrated in Figure 12.

It is noted that many of the starting materials employed in the synthetic methods described above are commercially available or are reported in the scientific literature.

In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α-ketoglutarate, and α-glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

The compounds of formula I can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, i.e., orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

Thus, the present compounds may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form must be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus

any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful dosages of the compounds of formula I can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

Generally, the concentration of the compound(s) of formula I in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%. Single dosages for injection, infusion or ingestion will generally vary between 50-1500 mg, and may be administered, i.e., 1-3 times daily, to yield levels of about 0.5 - 50 mg/kg, for adults.

Accordingly, the invention includes a pharmaceutical composition comprising a compound of formula I as described hereinabove; or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable diluent or carrier.

The ability of compounds of the invention to modulate PKC can be demonstrated using standard models which are well known in the art, or can be demonstrated using the tests described hereinbelow.

Isozyme Studies.

The isozyme selectivity of representative compounds of the invention and ILV (**3**) was determined by investigating their ability to displace [^{3}H]PDBU binding to recombinant PKC isozymes expressed in the baculovirus system, as described by Kazanietz, M. G.; et al. Characterization of ligand and substrate specificity for the calcium-dependent and calcium-independent PKC

isozymes. *Mol. Pharmacol.* **1993**, *44*, 298-307. As shown in Table 1, the compound of Example 1 (**17**) showed a higher affinity for the α and β isozymes, in comparison to γ, δ, and ε, with approximately a ten-fold difference in affinity between PKC α and ε. It is apparent that the ectronic effect of the acetylenic group influences isozyme selectivity, since the saturated alkyl compound of Example 2 (**18**) shows only a four-fold difference in the K_i for α versus ε.

Table 1. K_i values ± SEM for the inhibition of [^{3}H]PBDU binding by the compounds tested.

	α	β	γ	δ	ε
Compound					
Acetylene-Benzolactam 17	14.7 ± 1.3	17.4 ± 2.2	40.7 ± 8.9	122 ± 22	142 ± 3
Saturated-Benzolactam 18	46.6 ± 8.0	58.2 ± 12.6	145 ± 25	185 ± 30	187 ± 22
ILV*	11.0	6.1	19.4	8.2	21.9

*Data taken from *Mol. Pharmacol.* **1993**, *44*, 298-307.

Cell proliferation assay and PKC Downregulation.

Representative compounds of the invention were also tested for antiproliferative activity against breast carcinoma cell lines MCF-7 and MDA-MB-231 (Yu, G.; et al. Transfection with protein kinase Cα confers increased multidrug resistance to MCF-7 cells expressing P-glycoprotein. *Cancer Commun.* **1991**, *3*, 181-189). Exposure of MCF-7 and MDA-MB-231 cells to the compound of Example 1 (**17**) for four days resulted in IC_{50} values of 20 and 30 μM, respectively, whereas ILV (**3**) was inactive (Figure 13).

PKC isozyme levels were determined in MCF-7 and MDA-MB-231 cells exposed to the compound of Example 1 (**17**) for 24 hours (Figure 14). In MCF-7 cells, PKCβ and PKCε were virtually eliminated, PKCδ was reduced to a lesser extent, and PKCζ was unchanged. MDA-MB-231 cells exhibited a

similar reduction in PKCβ, whereas PKCδ and ζ were slightly reduced, while PKCα and PKCε remained unchanged. These results indicate that the compound of Example 1 (**17**), while not completely selective, preferentially downregulates PKCβ in both cell lines. The varying degree of selectivity of the compound of Example 1 for other PKC isozymes was to some degree cell type specific. This result was not completely unexpected, since different tumors would be expected to exhibit different PKC isozyme patterns as well as different pathways governing their stability and turnover.

Using a procedure similar to that described in: Price, J.E., et al. Cancer Res. 50:717-721, 1990, the antitumor activity of compound **17** was evaluated *in vivo* in MDA-MB-231 human breast carcinoma xenographs at the maximum dose evaluated thus far for toxicity, but not necessarily the maximum tolerated dose (Figure 15). Daily i.p. administration of the compound for three consecutive weeks resulted in 65% inhibition of tumor growth three weeks after treatment was initiated. No overt general cytotoxic effects were observed.

Compounds of the invention have been shown to be downregulators of PKC, and are therefore useful to treat conditions ameliorated by reduction of PKC activity. Such conditions include but are not limited to cancer, autoimmune diseases, and inflammation. Accordingly, the invention includes a method for modulating PKC in a mammal comprising administering to said mammal a pharmaceutically effective dose of a compound of formula I; or a pharmaceutically acceptable salt thereof. The invention also includes a method for the treatment of cancer in a mammal comprising administering to said mammal a pharmaceutically effective dose of a compound of formula I; or a pharmaceutically acceptable salt thereof.

Compounds of formula (I) are generally effective to treat mammalian conditions associated with pathological cellular proliferation. In addition to the utilities described above, they may also be useful to treat conditions which include restenosis, atherosclerosis, coronary heart disease, thrombosis, myocardial infarction, stroke, uterine fibroid or fibroma, and obliterative disease of vascular grafts and transplanted organs.

The invention will now be illustrated by way of the following non-limiting Examples.

Examples

Example 1. (2*S*,5*S*)-8-(1-Decynyl)benzolactam (Figure 11, compound **17**).

To a mixture of **16** (Figure 11) (116 mg, 0.27 mmol), Et_2NH (2 mL), and $PdCl_2(PPh_3)_2$ (26 mg, 0.018 mmol) were added 1-decyne (0.13 mL, 0.74 mmol) and CuI (4 mg, 0.01 mmol). The resulting solution was stirred at room temperature for 24 hours. The solvent was evaporated, the residue was dissolved in 1 mL of 20% aqueous NaOH and 4 mL of MeOH, and the solution was stirred at room temperature for 0.5 hours. The mixture was partitioned between 10 mL of water and 100 mL of EtOAc. The organic layer was separated, washed with brine, and dried over Na_2SO_4. Evaporation and chromatography on silica gel (2/1 ethyl acetate/petroleum ether as eluent) afforded 87 mg (81%) of the title compound (**17**): $[\alpha]^{20}_D$ -303.3° (*c* 0.5, ethanol); ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, *J* = 7.8 Hz, 1H), 7.09 (s, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.55 (s, 1H), 3.82 (m, 1H), 3.58 (m, 1H), 3.48 (m, 2H), 3.12 (dd, *J* = 16.3, 8.1 Hz, 1H), 2.80 (s, 3H), 2.73 (d, *J* = 16.2 Hz, 1H), 2.33 (m, 1H), 2.30 (t, *J* = 7.8 Hz, 2H), 1.68-1.15 (m, 12H), 1.05 (d, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.85 (d, *J* = 7.2 Hz, 3H); MS *m/z* 398 (M^+), 312, 91; HRMS calc. for $C_{25}H_{38}N_2O_2$ 398.293, found 398.294. Anal. calcd. for $C_{25}H_{38}N_2O_2$: C, 75.34; H, 9.61; N, 7.03. Found: C, 74.98, H, 9.86; N, 6.71.

The intermediate **16** was prepared as follows (Figure 11).

a. (*S*)-*O*-Acetyl-2-[(ethoxycarbonyl)amino]-3-phenyl-1-propanol (Figure 11, compound **78**). To a suspension of (*S*)-2-amino-3-phenyl-1-propanol **77** (25.0 g, 0.165 mol) and Na_2CO_3 (20.1 g, 0.19 mol) in 80 mL of water was added EtOCOCl (26.0 mL, 0.27 mol) dropwise at room temperature. The solution was stirred at room temperature for 4 hours and extracted with CH_2Cl_2 (4 x 250 mL). The organic layer was dried over Na_2SO_4 and evaporated to give an oil which was dissolved in Et_3N (100 mL, 0.72 mol) and Ac_2O (60 mL, 0.58 mol). The

mixture was stirred overnight at room temperature and partitioned between 400 mL of EtOAc and 150 mL of water. The organic layer was washed with 50 mL of brine and dried over Na_2SO_4. Evaporation and chromatography (1/2 ethyl acetate-petroleum ether as eluent) afforded 40.2 g (91%) of the di-acetate: $[\alpha]^{20}_D$ -17.9° (*c* 0.9, $CHCl_3$); IR (KBr) 2980, 1700, 1500, 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.15 (m, 4H), 4.72 (br s, 1H), 4.09 (q, *J* = 7.3 Hz, 2H), 4.07-4.02 (m, 3H), 2.80 (m, 2H), 2.04 (s, 3H), 1.18 (t, *J* = 7.3 Hz, 3H); MS *m/z* 265 (M^+), 165, 91. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.36; H, 7.30; N, 5.06.

b. (*S*)-*O*-Acetyl-3-(2-aminophenyl)-2-[(ethoxycarbonyl)amino]-1-propanol (Figure 11, compound **9**). To a solution of (*S*)-*O*-Acetyl-2-[(ethoxycarbonyl)amino]-3-phenyl-1-propanol (25.0 g, 0.094 mol) in Ac_2O (25 mL) was added nitric acid (10 mL, 0.24 mol) dropwise at 0 °C. The mixture was stirred at room temperature for 24 hours, poured into 200 mL of ice-water, and extracted with EtOAc (3 x 250 mL). The organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was dissolved in 200 mL of EtOAc, and 500 mg of Pd/C was added. The mixture was stirred under 1 atm of H_2 at room temperature for 24 hours. Filtration from the catalyst, evaporation, and chromatography (2/3 ethyl acetate/petroleum ether as eluent) provided **9** (6.02 g, 23%) and its isomer **10** (13.2 g, 50%). Compound **9**: $[\alpha]^{20}_D$ +4.6° (*c* 0.5, $CHCl_3$); IR (KBr) 3360, 1720, 1700, 1500, 1200, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.67 (m, 2H), 5.26 (br s, 1H), 4.14 (q, *J* = 7.3 Hz, 2H), 4.10-4.05 (m, 3H), 4.01 (br s, 2H), 2.94 and 2.61 (ABq, 2 H, *J* = 13.6 Hz), 2.10 (s, 3H), 1.25 (t, *J* = 7.3 Hz, 3H); MS *m/z* 280 (M^+), 191, 132, 106. Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.98; H, 7.19; N, 9.99. Found: C, 59.65; H, 7.19; N, 9.89.

c. (2*S*,2'*S*)-*N*-[3'-Acetoxy-2'-((ethoxycarbonyl)amino)phenyl]valine benzyl ester (Figure 11, compound **12**). A mixture of (*R*)-benzyl α-[[(trifluoromethyl)-sulfonyl]oxy]isovalerate (**11**, 5.03 g, 18.1 mmol), **9** (5.02 g, 18.1 mmol), and

2,6-lutidine (2.4 mL, 20 mmol) in 40 mL of 1,2-dichloroethane was stirred at 70 °C for 10 hours. Evaporation and chromatography on silica gel (1/5 ethyl acetate/petroleum as eluent) gave compound **12** (6.05g, 70%) as a colorless oil: $[\alpha]^{20}_D$ -20.6° (*c* 0.07, $CHCl_3$); IR (KBr) 3300, 1725, 1710, 1520 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 5H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.67 (t, *J* = 7.5 Hz, 1H), 6.68 (d, *J* = 7.6 Hz, 1H), 5.14 (m, 3H), 4.12 (m, 5H), 3.91 (d, *J* = 6.2 Hz, 1H), 2.98 (m, 1H), 2.67 (m, 1H), 2.23 (m, 1H), 2.02 (s, 3H), 1.16 (t, *J* = 7.2 Hz, 3H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H); MS *m/z* 471 (M + H^+), 335, 275, 186, 91; HRMS calcd for $C_{26}H_{34}N_2O_6$ 470.241; found 470.241.

d. (2*S*,5*S*)-Benzolactam (Figure 11, compound **15**). A mixture of **12** (6.0 g, 12.8 mmol) and KOH (5.0 g, 89 mmol) in 40 mL of MeOH/H_2O (1:1) was stirred at 30 °C for 3 days. After neutralization to pH approx. 7 with conc. HCl, di-*tert*-butyl dicarbonate (2.7 g, 12.5 mmol) and $NaHCO_3$ (1.5 g, 18 mmol) were added. The mixture was stirred at room temperature for 24 hours, washed with petroleum ether, and adjusted to approximately pH 2. Extraction with EtOAc (4 x 150 mL), drying over Na_2SO_4, and evaporation gave 4.1 g of crude **13**. This product (1.61g, 4.37 mmol) and *N*-hydroxysuccinimide (0.52 g, 4.41 mmol) were dissolved in 20 mL of CH_3CN. Dicyclohexylcarbodiimide (DCC) (1.21 g, 5.81 mmol) in 20 mL of CH_3CN was added dropwise at 0 °C, and the mixture was stirred at room temperature overnight. Filtration from the precipitate, evaporation, and chromatography on silica gel (1/1 CH_2Cl_2/EtOAc as eluent) provided 1.79 g of **14**. Without further purification, this product was directly dissolved in 10 mL of dried CH_2Cl_2, and the solution was cooled to 0 °C before 10 mL of CF_3COOH was added. The mixture was stirred at 0 °C for 2 hours, and the volatiles were removed in vacuo below 30 °C. The residue was dissolved in 100 mL of EtOAc, and 5 mL of saturated aqueous $NaHCO_3$ solution was added. The mixture was heated at 80 °C for 24 hours with vigorous stirring. After cooling to room temperature, 40 mL of water was added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (4 x 20 mL). Drying

over Na_2SO_4 and evaporation produced a yellow oil, which was dissolved in 10 mL of CH_3CN. This solution was cooled to 0 °C, and 4.0 mL (40 mmol) of formalin, 1.0 g (16 mmol) of $NaBH_3CN$, and 0.27 mL of AcOH were added. The resulting mixture was stirred at 0 °C for 2 hours before quenching with phosphate buffer (pH = 2). The solvent was evaporated, and the residue was dissolved in EtOAc, washed with water, saturated $NaHCO_3$, and brine, and dried over Na_2SO_4. Evaporation and chromatography on silica gel (1/10 MeOH/CH_2Cl_2 as eluent) gave **15** (480 mg, 44% overall from **12**): $[\alpha]^{20}_D$ -271° (*c* 0.08, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.80-7.20 (m, 4H), 6.72 (br s, 1H), 4.10 (m, 1H), 3.73 (m, 1H), 3.61 (m, 1H), 3.46 (d, J = 8.1 Hz, 1H), 3.11 (dd, J = 15.8, 8.1 Hz, 1H), 2.85 (dd, J = 15.8, 3.2 Hz, 1H), 2.84 (s, 3H), 2.48 (m, 1H), 1.15 (d, J = 6.4 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H); MS *m/z* 262 (M^+), 245, 117, 91.

e. (2*S*,5*S*)-8-Iodobenzolactam (Figure 11, compound **16**). A mixture of **15** (850 mg, 3.2 mmol), Et_3N (15 mL), and Ac_2O (5 mL) was stirred at room temperature for 24 hours. The mixture was poured into 100 mL of water, extracted with EtOAc (4 x 100 mL), washed with brine, and dried over Na_2SO_4. After evaporation, the residue was dissolved in 10 mL of 1,4-dioxane and 2 mL of pyridine. To this solution 1.70 g (6.7 mmol) of I_2 was added, and the deep brown solution was stirred at room temperature for 3 days. The mixture was partitioned between EtOAc and water, and the organic layer was washed with 10 mL of 10% aqueous $NaHSO_3$ and dried over Na_2SO_4. Chromatography on silica gel provided 598 mg of **16** together with 338 mg of unreacted starting material (83% of **16** based on conversion): $[\alpha]^{20}_D$ -279° (*c* 0.21, $CHCl_3$); IR (KBr) 3200, 1740, 1680, 1260, 1240, 1065 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18-7.00 (m, 3H), 6.05 (s, 1H), 4.54 (m, 1H), 4.13 and 3.98 (ABq, 2 H, J = 11.1 Hz, both parts d with J = 8.2 Hz), 3.45 (d, J = 8.2 Hz, 1H), 3.01-2.87 (m, 2H), 2.76 (s, 3H), 2.46 (m, 1H), 2.10 (s, 3H), 1.08 (d, J = 7.2 Hz, 3H), 0.92 (d, J = 7.2 Hz, 3H); MS *m/z* 430 (M^+), 304, 261, 233, 158, 132; HRMS calcd for $C_{17}H_{23}N_2O_3I$: 430.076, found: 430.075.

Example 2. (2*S*,5*S*)-8-Decylbenzolactam (Figure 11, compound **18**).

A mixture of the compound of Example 1 (**17**) (20 mg, 0.05 mmol), Pd/C (10 mg), and EtOAc (5 mL) was hydrogenated under 10 atm of H_2 at room temperature for 2 hours. Filtration from the catalyst, evaporation, and chromatography gave 18 mg (90%) of the title compound **18**: $[\alpha]^{20}_D$ -247.5° (*c* 1.0, ethanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (m, 2H), 6.87 (s, 1H), 6.45 (s, 1H), 4.14 (m, 1H), 3.78 and 3.51 (ABq, 2H, J = 15.8 Hz, both parts d, J = 12.4 and 8.6 Hz, resp.), 3.39 (d, J = 8.3 Hz, 1H), 2.96 (dd, J = 16.2, 10.6 Hz, 1H), 2.83 (d, J = 16.2 Hz, 1H), 2.70 (s, 3H), 2.36 (t, J = 7.6 Hz, 2H), 2.30 (m, 1H), 1.60-1.06 (m, 16H), 1.01 (d, J = 7.6 Hz, 3H), 0.82 (d, J = 7.6 Hz, 3H), 0.79 (t, J = 7.4 Hz, 3H); MS *m/z* 402 (M^+), 359, 331, 316; HRMS calc. for $C_{25}H_{42}N_2O_2$ 402.324, found 402.325. Anal. calcd. for $C_{25}H_{42}N_2O_2$: C, 74.58; H, 10.51; N, 6.96. Found: C, 74.26, H, 10.82; N, 6.71.

Example 3. (2S,5S)-7-Methoxy-8-(1-decynyl) benzolactam (Figure 12, compound **8**).

To a suspension solution of **7**(Figure 12) (25 mg, 0.085 mmol) and $HgCl_2$ (23 mg, 0.085 mmol) in 2 mL of methylene chloride was added I_2 (22 mg, 0.085 mmol). The mixture was stirred at room temperature overnight and filtered. The filtrate was washed with aqueous 0.1 M sodium thiosulfate, and a saturated aqueous solution of potassium iodide. The organic layer was dried and concentrated by rotary evaporation.

To a mixture of the above iodide, 2 mL of diethylamine and $PdCl_2(Ph_3P)_2$ (13 mg. 0.009 mmol) was added 1-decyne (0.065 mL, 0.37 mmol) and CuI (4 mg, 0.01 mmol). The resulting solution was stirred at room temperature for 24 hours. The solvent was removed under reduced pressure, and the residual oil was purified by chromatography (silica gel, 2/1 ethyl acetate/petroleum ether as eluent) to afford 27 mg (74% yield) of the title compound **8**. $[\alpha]^{20}_D$ = -302° (c 0.63, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18

(d, J = 8.3 Hz, 1H), 6.70 (br s, 1H), 6.62 (d, J = 8.3 Hz, 1H), 3.89 (s, 3H), 3.72-3.53 (m, 3H), 3.46 (d, J = 9.2 Hz, 1H), 3. 26 and 2.78 (AB q, d, J = 17.3 Hz, 2H), 2.79 (s, 3H), 2.48 (t, J = 7.5 Hz, 2H), 2.46 (m, 1H), 1.53 (m, 2H), 1.46(m, 2H), 1.37 (m, 8H), 1.02 (d, J = 7.4 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H), 0.78 (d, J = 7.4 Hz, 3H): MS m/z 428 (M+), 329, 291, 249, 221, 104, 77. HRMS calcd for $C_{26}H_{40}N_2O_3$: 428.304, found: 428.302.

a) 3-Hydroxy-2-(hydroxymethyl)nitrobenzene (Figure 12, compound **80**). A mixture of 15.0 g of 5-nitro-1,3-benzodioxane**79** (Ando, M.; Emoto, S., Bull. Chem. Soc. Jpn. 46, 2093, **1973**) and 800 mL of 1 N HCl was allowed to reflux for 24 hours. The cooled suspension was extracted with ethyl acetate (400 mL x 3). The combined organic layers were washed with water and brine, and dried over $MgSO_4$. After removal of solvent, the residual oil was purified by chromatography to afford 9.7 g of the diol. ^{1}H NMR (300 MHz $CDCl_3$) δ 7.41 (d, J = 7.2 Hz, 1H), 7.28 (dd, J = 7.2 Hz, 1H), 7.13 d, J = 7.2 Hz), 5.09 (s, 2H); MS M/z 169 (M^+), 151, 133, 121, 105, 93, 77.

b) 2-(Hydroymethyl)-3-(methoxy)nitrobenzene (Figure 12, compound **81**). To a solution of 9.7 g of **80** (57 mmol) in 300 mL of dry acetone was added 81 g of idomethane (57 mmol) and 11.8 g of potassium carbonate (85 mmol). The mixture was allowed to reflux overnight, and the cooled solution was partitioned between 300 mL of ethyl acetate and 100 mL of water. The organic layer was washed with water and brine, and dried over Na_2SO_4. After removal of solvent, the residual oil was passed a short column (silica gel, 1/1 ethyl acetate/petroleum ether as eluent) to afford 10.3 g (98%) of the methoxy alcohol; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, J = 7.2 Hz, 1H), 7.19 (dd, J = 7.2 Hz, 1H), 7.09 (2, J = 7.2 Hz), 5.10 (s, 2H), 3.81 (s, 3H); MS m/z 183 (M+), 166, 150, 108, 92, 77; HRMS calcd for $C_8H_9NO_4$: 183.053, found: 183.052.

c) 2-[2-(tert-Butoxycarbonylamino)-2-(ethoxycarbonyl)ethyl]-3-(methoxy) nitrobenzene (Figure 12, compound 4). To a solution of **81** (4.0 g, 22 mmol) and

triethylamine (3.3 g, 33 mmol) in 160 mL of THF was added mesyl chloride (3.8 g, 33 mmol), dropwise with cooling at -20 °C. The solution was warmed to room temperature slowly, and the THF was removed by rotary evaporation. The residue was partitioned between 200 mL of ethyl acetate and 70 mL of water. The organic layer was washed with water and brine, and dried over Na_2SO_4. After removal of solvent, the residue was dried in vacuo and then this residue was dissolved in 50 mL of methylene chloride. To the resulting solution was added Bu_4NBr (6.16 g, 19.2 mmol), (5.0 g, 19.2 mmol) and 50 mL of 10% NaOH. The mixture was stirred for 36 hours at room temperature. The organic layer was separated and aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was dissolved in 50 mL of THF, and 50 mL of 5% HCl was added. The resulting solution was stirred overnight and then saturated aqueous $NaHCO_3$ was added to adjust pH to 11. After removal of the THF by rotary evaporation, the residue was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residual oil was dissolved in 60 mL of acetonitrile, and then 3.75 g of di-tert-butyl-dicarbonate (17.1 mmol) was added. After stirring overnight, the solution was concentrated and the residue was chromatographed to afford 3.80 g (49% yield from 3) of the ester. ^1H NMR (300 MHz, CDCl3) δ 7.41 (d, J = 7.2 Hz, 1H), 7.33 (dd, J = 7.2 Hz), 5.22 (br s, 1H), 4.36-4.10 (m, 3H), 3.92 (s, 3H), 3.04 (M, 2H), 1.01 (s, 9H), 0.99 (t, J + 7.2 Hz, 3H); MS m/z 368 (M+), 271, 150, 104, 77: HRMS calcd for $C_{17}H_{24}N_2O_7$; 368.159, found: 358.156.

d) 2-[2-(tert-Butoxycarbonylamino)-3-hydroxypropyl]-3-(methoxy)aniline (Figure 12, compound **5**). A mixture of **4** (5.0 g, 14.2 mmol), $NaBH_4$ (1.62g, 42.6 mmol) in 350 mL of dry ethanol was heated at reflux for 2 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was partitioned between 400 mL of ethyl acetate and 100 mL of water. The organic layer was separated, washed with water and brine, and dried

over Na_2SO_4. After removal of the solvent, the residual oil was chromatographed to afford the nitro-alcohol.

A suspension of the nitro-alcohol and 100 mg of 10% Pd/C in 100 mL of methanol was exposed to hydrogen under atmospheric pressure with vigorous stirring. After no more hydrogen was taken up, the Pd/C was filtered off, and the filtrate was concentrated. Chromatography of the residual oil afforded 3.65 g (92% yield) of **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ6.98 (dd, J = 7.2 Hz, 1H), 6.25 (d, J = 7.3 Hz, 1H), 6.20 (d, J + 7.2 Hz, 1H), 5.03 (br s, 1H), 4.88 (br, s, 1H), 4.18 (m, 1H), 3.79 (s, 3H), 3.29 and 3.18 (AB q, d, J = 7.8 Hz, 2H), 2.85 and 2.74 (AB q, d, J = 15.4 Hz, 2H), 1.44 (s, 9H); MS m/z 296 (M+), 104, 77: HRMS calcd for $C_{15}H_{24}N_2$)(4: 296.174 found: 296.171.

e) N-[(S)-1-Ethoxycarbonyl-2-methylbutyl]-2-[2-(tert-butoxycarbonylamino)-3-hydroxypropyl]-3-(methoxy)aniline (Figure 12, compound **6**). To a solution of (R)-ethyl-α-[[(trifluoromethyl)sulfonyl]oxy] isovalerate (2.9 g, 10.5 mmol), **5** (2.8 g, 10 mmol in 35 mL of 1,2-dichloroethane was added 2,6-lutidine (1.87 g, 11 mmol). The resulting solution was heated at 70 °C for 40 hours, and the cooled solution was directly chromatographed to afford 2.46 g (67%) of **6**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (dd, J = 7.2 Hz, 1H), 6.30 (d, J = 7.2 Hz, 1H), 6.23 (d, J = 7.2 Hz) 5.29 ()br, s, 1H), 4.11 (m, 3H), 3.84-3.44 (m, 2H), 3.79 (s, 3H), 2.98-2.72 (m, 2H), 1.86 (m, 1H), 1.43 (s, 9H), 1.34-0.88 (m, 9H).

f) (2S,5S)-7-Methoxybenzolactam (Figure 12, compound **7**). A mixture of **6** (2.1 g, 5.15 mmol), 20 mL of 0.5 N aqueous NaOH, and 20 mL of ethanol was stirred for 10 hours at room temperature. The resulting solution was neutralized to a pH of ~5 with concentrated hydrochloride acid and extracted with ether to afford 1.52 g of crude acid.

This acid (1.5 g, 4.0 mmol) and N-hydroxysuccinimide (1.2 g, 10.0 mmol) were dissolved in 20 mL of acetonitrile. To this solution DCC (1.5 g, 7.5 mmol) in 20 mL of acetonitrile was added dropwise at 0 °C. The mixture

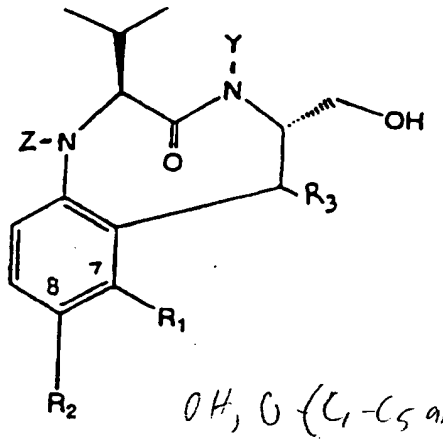
was stirred at room temperature overnight. After filtering off the resulting solid, the solution was evaporated under reduced pressure, and the residue was chromatographed on silica gel (1/1 methylene chloride/ethyl acetate as eluent) to provide 1.34 g of the activated ester. Without further purification, this product was directly dissolved in 10 mL of dried methylene chloride, and the resulting solution was cooled at 0 °C prior to the addition of 10 mL of trifluoroacetic acid. The reaction mixture was stirred at 0 °C for 2 hours, and the trifluoroactic acid was removed in vacuo at below 30 °C. The residue was dissolved in 100 mL of ethyl acetate and 10 mL of a saturated aqueous $NaHCO_3$ solution. The mixture was heated at 80 °C for 24 hours with vigorous stirring. After cooling to room temperature, 40 mL of water was added to the mixture, and the mixture was extracted with ethyl acetate (4 x 100 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was dissolved in 10 mL of acetonitrile, and 4 mL (40 mmol) of formalin, 1.0 g (16 mmol) of sodium cyanoborohydride, and 0.27 mL of acetic acid were added sequentially at 0 °C. The resulting solution was stirred at 0 °C for 2 hours. After quenching with phosphate buffer (pH = 2), the solvent was removed by evaporation. The residue was dissolved in ethyl acetate, and the solution was washed with water, saturated sodium bicarbonate, and brine, and dried over Na_2SO_4. After concentration, the residue was purified by chromatography on silica gel (9/1 ethyl acetate/methylene chloride as eluent) to give **7** (280 mg, 20% overall yield from **6**). $[\alpha]^{20}_D = -252°$ (c 1.3, $CHCl_3$); H NMR (300 MHz, $CDCl_3$) δ 7.15 (dd, J = 8.1 Hz, 1H), 6.83 (br s, 1H), 6..67 (d, J = 8.1 Hz, 1H), 6.51 (d, J = 8.1 Hz, 1H), 3.92 (m, 1H), 3.82 (s, 3H), 3.75-3.18 (m, 4H), 2.78 (s, 3H), 2.70 (m, 1H), 2.38 (m, 1H), 1.08 (d, J = 7.2 Hz, 3H), (d, J = 7.2 Hz, 3H); MS m/z 292 (M^+), 261, 249, 221, 174, 162, 137, 114; HRMS calcd for $C_{16}H_{24}N_2O_3$: 292.179, found: 292.173.

All patents, patent applications, and publications cited herein, and specifically, U.S. Provisional Patent Application Number 60/017,532, are incorporated by reference herein as though fully set forth.

CLAIMS

What is claimed is:

1. A compound of formula I:



(I)

wherein

R_1 is H, $(C_1$-$C_5)$alkyl, OR^a, SR^a, $N(R^a)(R^b)$, halo, NO_2, $NHC(O)[(C_1$-$C_4)$alkyl] or NHOH;

R_2 is a $(C_5$-$C_{22})$ hydrocarbyl group, optionally comprising 1-3 double bonds, 1-2 triple bonds or a mixture thereof, or $(C_6$-$C_{12})$aryl$(C_2$-$C_{10})$alkyl, wherein the alkyl moiety optionally comprises 1-2 double bonds, 1-2 triple bonds or a mixture thereof; wherein said $(C_5$-$C_{22})$ hydrocarbyl group or said $(C_6$-$C_{12})$aryl$(C_2$-$C_{10})$alkyl may optionally be substituted with 1 or 2 substituents independently selected from the group consisting of halo, hydroxy, cyano, nitro, $(C_1$-$C_5)$alkyl, $(C_1$-$C_5)$alkoxy, trifluoromethyl, trifluoromethoxy, $-C(=O)O(C_1$-$C_5)$alkyl, and $N(R^e)(R^f)$;

R_1 and R_2 together are $-CH(R^c)-CH_2-C(O)-N(R^d)-$, $-C(R^c)=CH-C(O)N(R^d)-$, $-C(R^c)=CH-N(R^d)-$ or $-C(R^c)=CH-O-$;

R_3 is H, OH or halo;

R^a and R^b are independently H or $(C_1$-$C_5)$alkyl;

R^c is a $(C_5$-$C_{22})$ hydrocarbyl group;

R^d is H or $(C_1$-$C_5)$alkyl

R^e and R^f are independently hydrogen, $(C_1$-$C_5)$alkyl, or $(C_1$-$C_5)$alkanoyl, or together with the nitrogen to which they are attached are pyrrolidino, piperidino or morpholino;

Z is H or (C_1-C_5)alkyl; and

Y is H or (C_1-C_5)alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 wherein:

R_1 is OR^a, SR^a, $N(R^a)(R^b)$, halo, NO_2, NHC(O)[(C_1-C_4)alkyl] or NHOH; and

R_2 is a (C_5-C_{22}) hydrocarbyl group, optionally comprising 1-3 double bonds, 1-2 triple bonds or a mixture thereof, or (C_6-C_{12})aryl(C_2-C_{10})alkyl, wherein the alkyl moiety optionally comprises 1-2 double bonds, 1-2 triple bonds or a mixture thereof; or

R_1 and R_2 together are -$CH(R^c)$-CH_2-C(O)-$N(R^d)$-, -$C(R^c)$=CH-C(O)$N(R^d)$-, -$C(R^c)$=CH-$N(R^d)$- or -$C(R^c)$=CH-O-.

3. A compound of claim 1 wherein (C_1-C_5)alkyl is methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, or cyclopentyl; and aryl is phenyl, methylphenyl, ethylphenyl, propylphenyl, dimethylphenyl, diethylphenyl, indenyl, methylindenyl, dimethylindenyl, naphthyl, methylnaphthyl, or dimethylnaphthyl.

4. A compound of claim 1 wherein R_1 is OR^a, SR^a, $N(R^a)(R^b)$, halo, NO_2, NHC(O)[(C_1-C_4)alkyl] or NHOH.

5. A compound of claim 1 wherein R_1 is OR^a.

6. A compound of claim 1 or 2 wherein R_2 is 1-decyl or 1-decynyl.

7. A compound of claim 1 or 2 wherein R_3 is H.

8. A compound of claim 1 or 2 wherein R^c is (C_5-C_{15})alkyl.

9. A compound of claim 1 or 2 wherein Y is H.

10. A compound of claim 1 or 2 wherein Z is methyl.

11. A compound of claim 1 wherein R_1 and R_2 together are -CH(R^c)-CH_2-C(O)-N(R^d)-, -C(R^c)=CH-C(O)N(R^d)-, -C(R^c)=CH-N(R^d)- or -C(R^c)=CH-O-.

12. A compound of claim 1 wherein Z is CH_3; Y is H; R_1 is OR^a, SR^a, N(R^a)(R^b), halo, NO_2, NHC(O)[(C_1-C_4)alkyl] or NHOH; R_2 is (C_5-C_{15})alkyl, optionally comprising 1-3 double bonds, 1-2 triple bonds or a mixture thereof; and R_3 is H; or a pharmaceutically acceptable salt thereof.

13. A compound of claim 1 or 2 wherein Z is CH_3; Y is H; R_2 is (C_5-C_{15})alkyl, optionally comprising 1-3 double bonds, 1-2 triple bonds or a mixture thereof; and R_3 is H; or a pharmaceutically acceptable salt thereof.

14. A compound of claim 1 or 2 wherein R_2 is 1-decynyl.

15. A compound of claim 1 or 2 wherein R_2 is (C_5-C_{15})alkyl, optionally comprising 1-3 double bonds, 1-2 triple bonds or a mixture thereof.

16. A compound of claim 1 or 2 wherein R_2 is (C_6-C_{12})aryl(C_2-C_{10})alkyl, wherein the alkyl moiety optionally comprises 1-2 double bonds, 1-2 triple bonds or a mixture thereof.

17. A compound of claim 1 which is (2*S*,5*S*)-8-(1-decynyl)-benzolactam **17**; or a pharmaceutically acceptable salt thereof.

18. A compound of claim 1 which is (2*S*,5*S*)-8-decylbenzolactam **18**; or a pharmaceutically acceptable salt thereof.

19. A compound of claim 1 which is (2S,5S)-7-methoxy-8-(1-decynyl) benzolactam 8; or a pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition comprising an amount of the compound of claim 1 effective to inhibit pathological proliferation of mammalian cells, in combination with a pharmaceutically acceptable carrier.

21. A therapeutic method to treat a condition characterized by the pathological proliferation of mammalian cells comprising administering to a mammal afflicted with such a condition, an effective amount of a compound of claim 1.

22. The method of claim 21 wherein the condition is a cancer.

23. A method for modulating PKC in a mammal comprising administering to said mammal a pharmaceutically effective dose of a compound of formula I; or a pharmaceutically acceptable salt thereof.

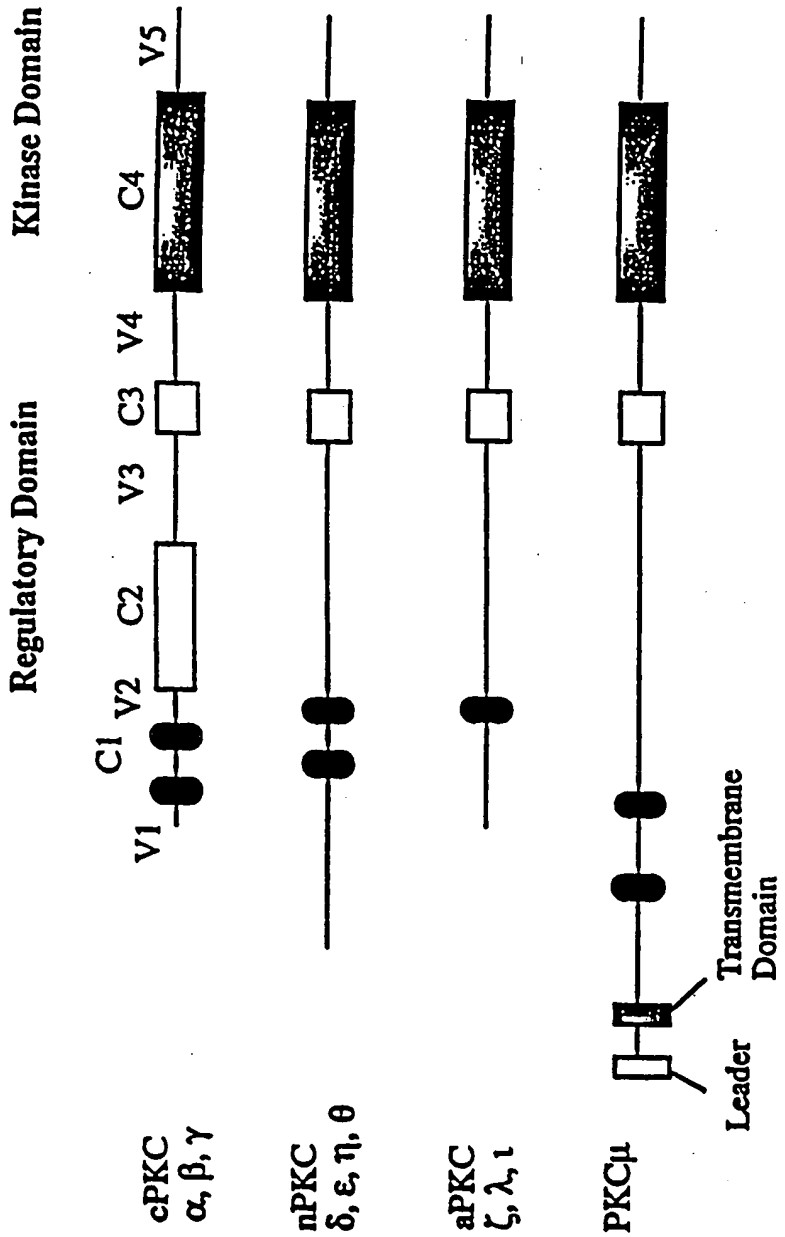

Regulatory Domain
Kinase Domain
C1
V1
V2
C2
V3
C3
V4
C4
V5
cPKC
α, β, γ
nPKC
δ, ε, η, θ
aPKC
ζ, λ, ι
PKCμ
Transmembrane Domain
Leader

FIG. 1

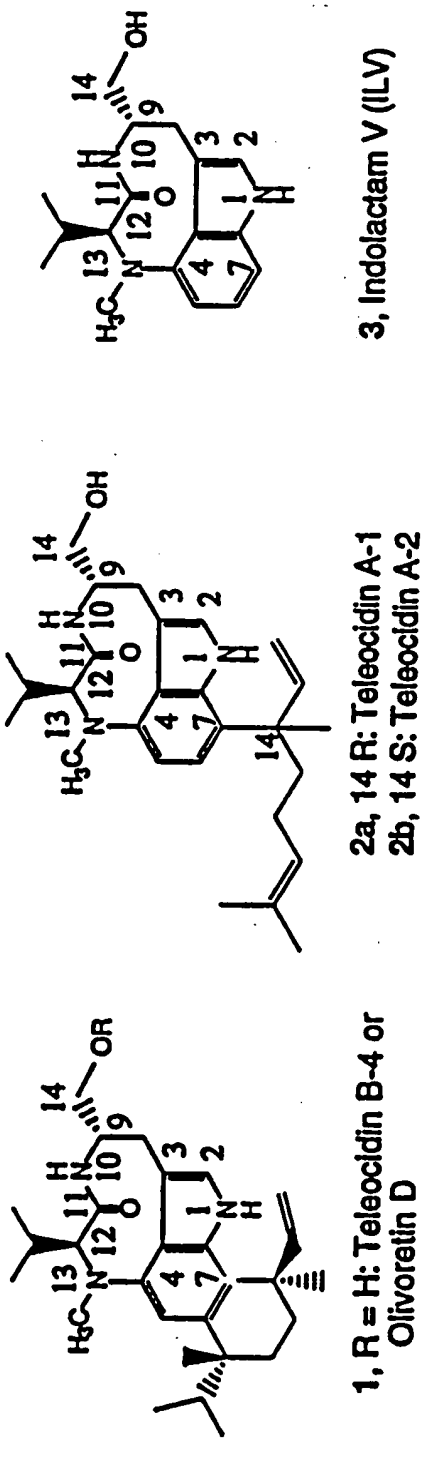
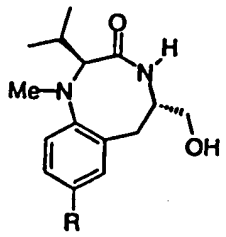

1, R = H: Teleocidin B-4 or Olivoretin D
2a, 14 R: Teleocidin A-1
2b, 14 S: Teleocidin A-2
3, Indolactam V (ILV)

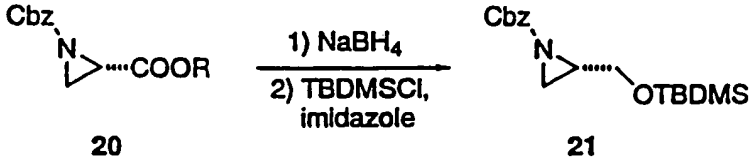
FIG. 2



17 , R = $-C\equiv C(CH_2)_7CH_3$

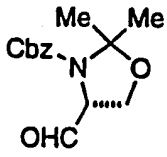
18 , R = $-(CH_2)_8CH_3$

FIG. 3



20 **21**

FIG. 4



23

FIG. 5

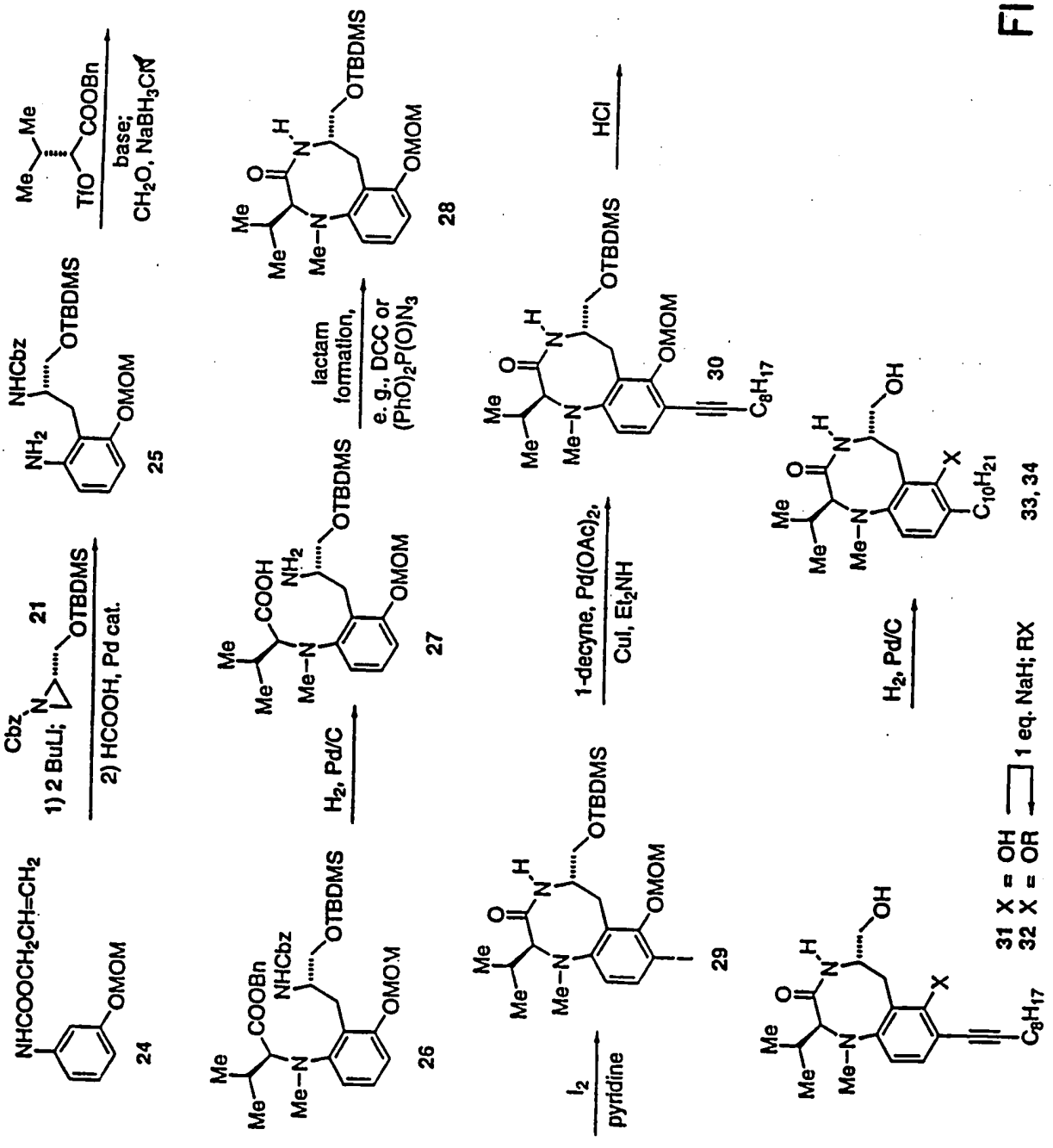

NHCOOCH2CH=CH2
OMOM
24
1) 2 BuLi;
2) HCOOH, Pd cat.
21
OTBDMS
Cbz
N
NHCbz
NH2
OTBDMS
OMOM
25
TfO
COOBn
base;
CH2O, NaBH3CN
Me
Me
H2, Pd/C
COOBn
NHCbz
OTBDMS
OMOM
26
lactam formation,
e.g., DCC or (PhO)2P(O)N3
COOH
NH2
OTBDMS
OMOM
27
OTBDMS
OMOM
28
I2
pyridine
OTBDMS
OMOM
29
1-decyne, Pd(OAc)2,
CuI, Et2NH
OTBDMS
OMOM
C8H17
30
HCl
H2, Pd/C
OH
X
C10H21
33, 34
31 X = OH
32 X = OR
1 eq. NaH; RX
OH
X
C8H17

FIG. 6

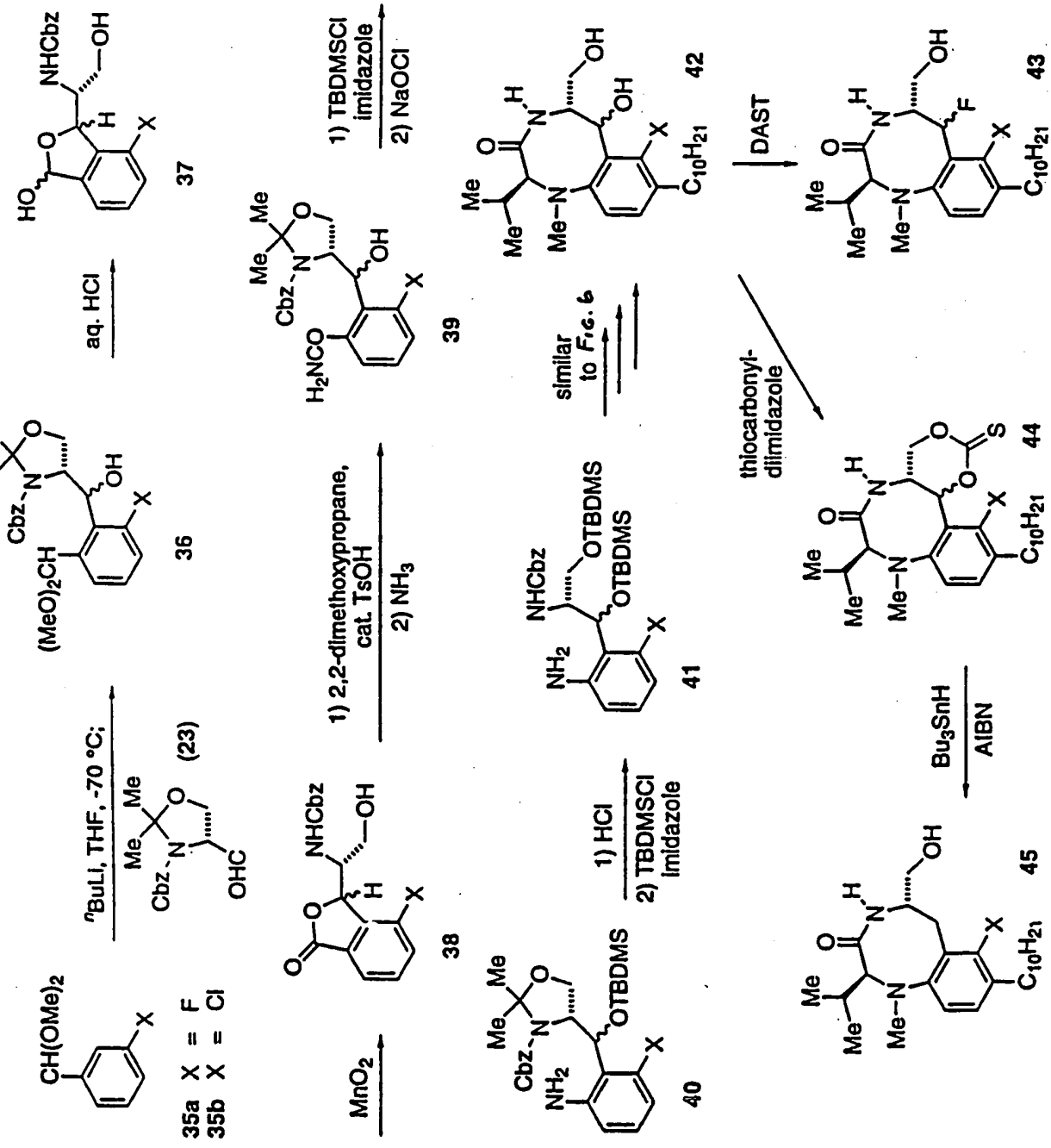

CH(OMe)2
X
35a X = F
35b X = Cl
nBuLi, THF, -70 °C;
Me
Me
Cbz
N
O
OHC
(23)
(MeO)2CH
Me
Me
Cbz
N
O
OH
X
36
aq. HCl
HO
NHCbz
OH
H
X
37
MnO2
NHCbz
OH
H
X
38
1) 2,2-dimethoxypropane, cat. TsOH
2) NH3
Me
Me
Cbz
N
O
OH
H2NCO
X
39
1) TBDMSCl imidazole
2) NaOCl
1) HCl
2) TBDMSCl imidazole
Me
Me
Cbz
N
O
OTBDMS
NH2
X
40
NHCbz
OTBDMS
NH2
X
41
similar to Fig. 6
Me
N
H
O
OH
OH
Me
Me–N
X
C10H21
42
DAST
Me
N
H
O
OH
F
Me
Me–N
X
C10H21
43
thiocarbonyl-diimidazole
Me
N
H
O
O
O
S
Me
Me–N
X
C10H21
44
Bu3SnH
AIBN
Me
N
H
O
OH
Me
Me–N
X
C10H21
45

FIG. 7

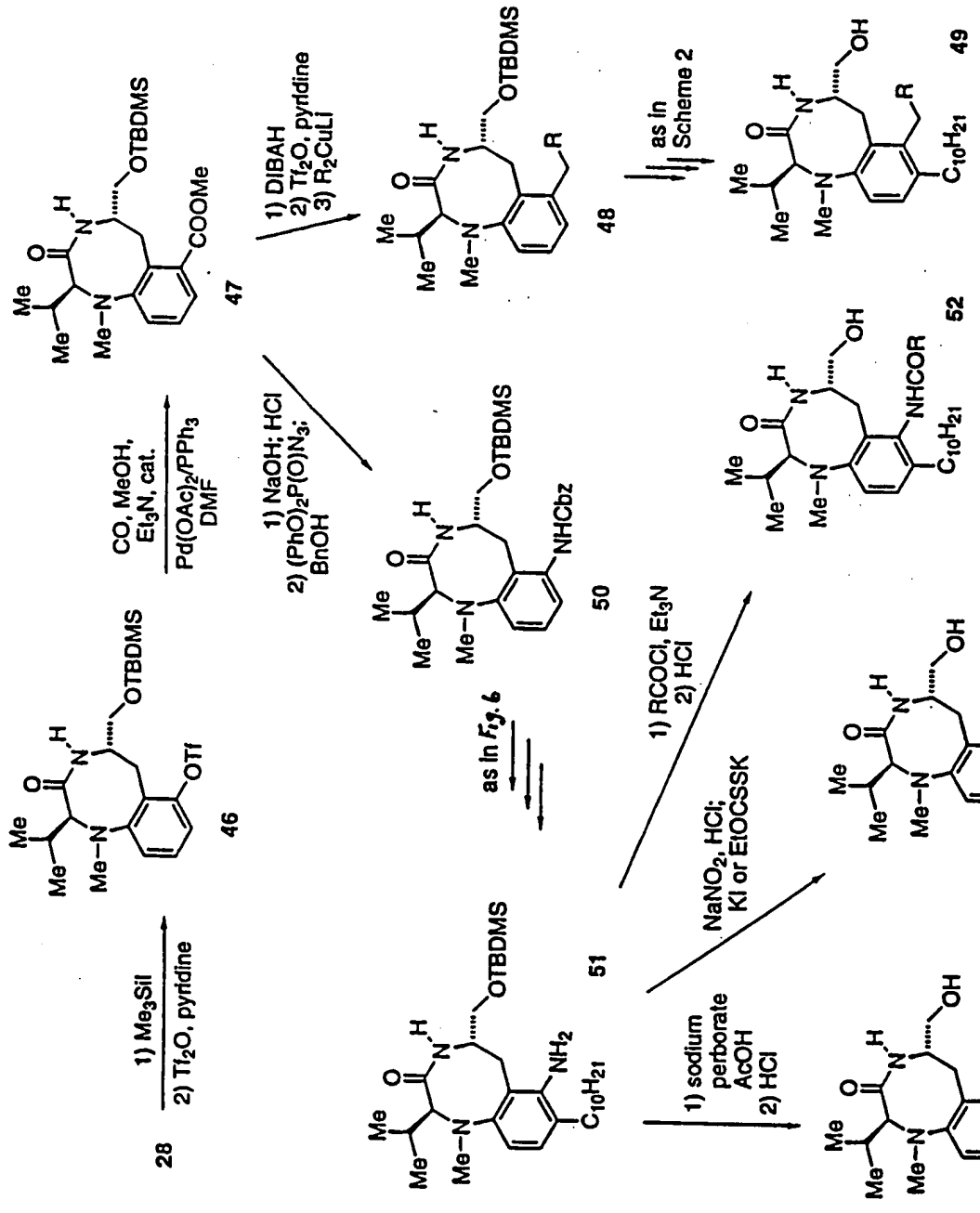

1) Me3SiI
2) Tf2O, pyridine
CO, MeOH, Et3N, cat.
Pd(OAc)2/PPh3 DMF
1) DIBAH 2) Tf2O, pyridine 3) R2CuLi
1) NaOH; HCl 2) (PhO)2P(O)N3; BnOH
as in Fig. 6
as in Scheme 2
1) RCOCl, Et3N 2) HCl
NaNO2, HCl; KI or EtOCSSK
1) sodium perborate AcOH 2) HCl
Zn, NH4Cl
NaOH
28
46
47
48
49
50
51
52
53 X = NO2
54 X = NHOH
55 X = I
56 X = SC(S)OEt
57 X = SH

FIG. 8

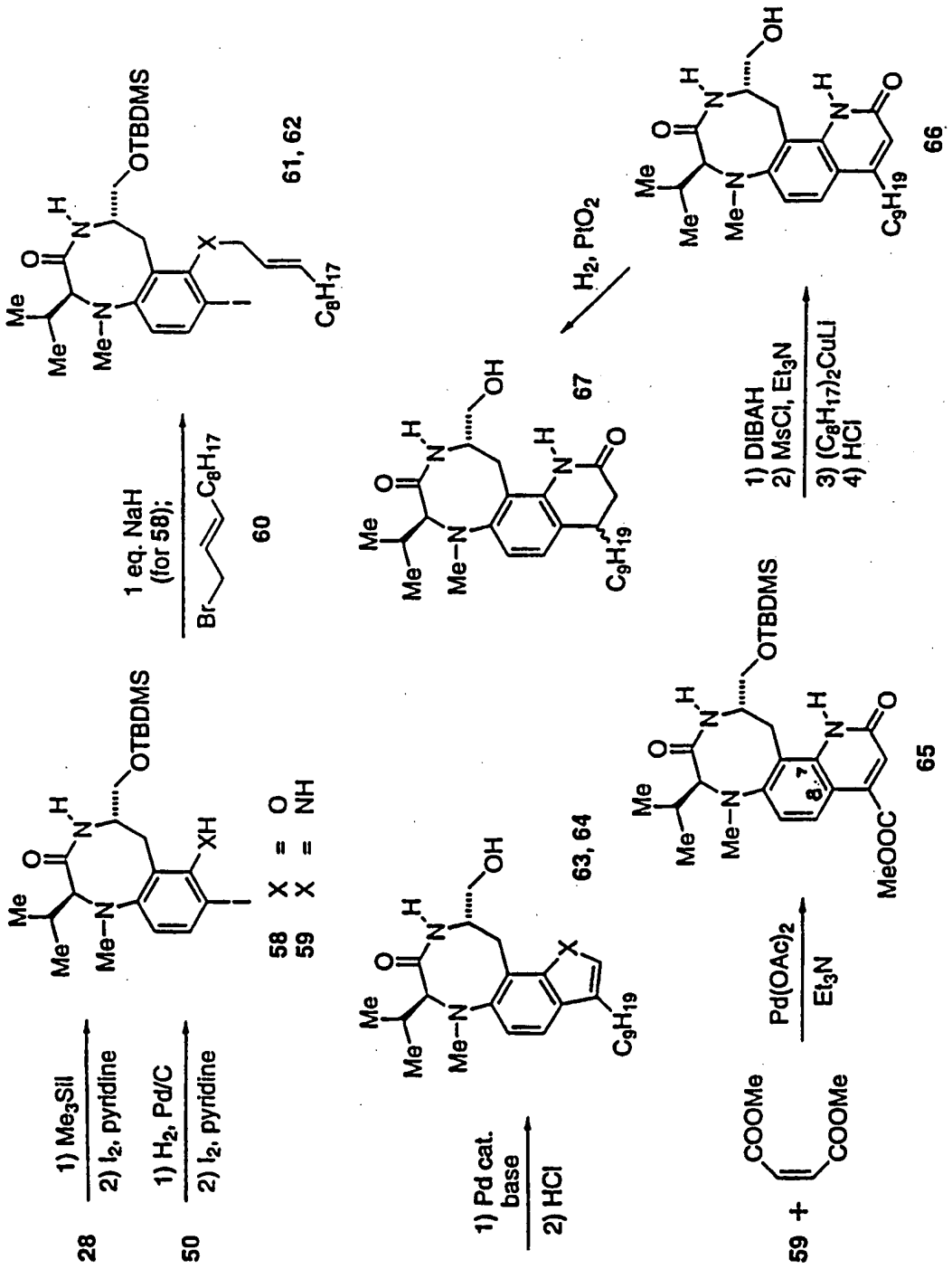

28
1) Me3Sil
2) I2, pyridine
50
1) H2, Pd/C
2) I2, pyridine
58 X = O
59 X = NH
1 eq. NaH
(for 58);
60
61, 62
1) Pd cat.
base
2) HCl
63, 64
H2, PtO2
67
66
1) DIBAH
2) MsCl, Et3N
3) (C8H17)2CuLi
4) HCl
59 +
Pd(OAc)2
Et3N
65
MeOOC
COOMe
COOMe

FIG. 9

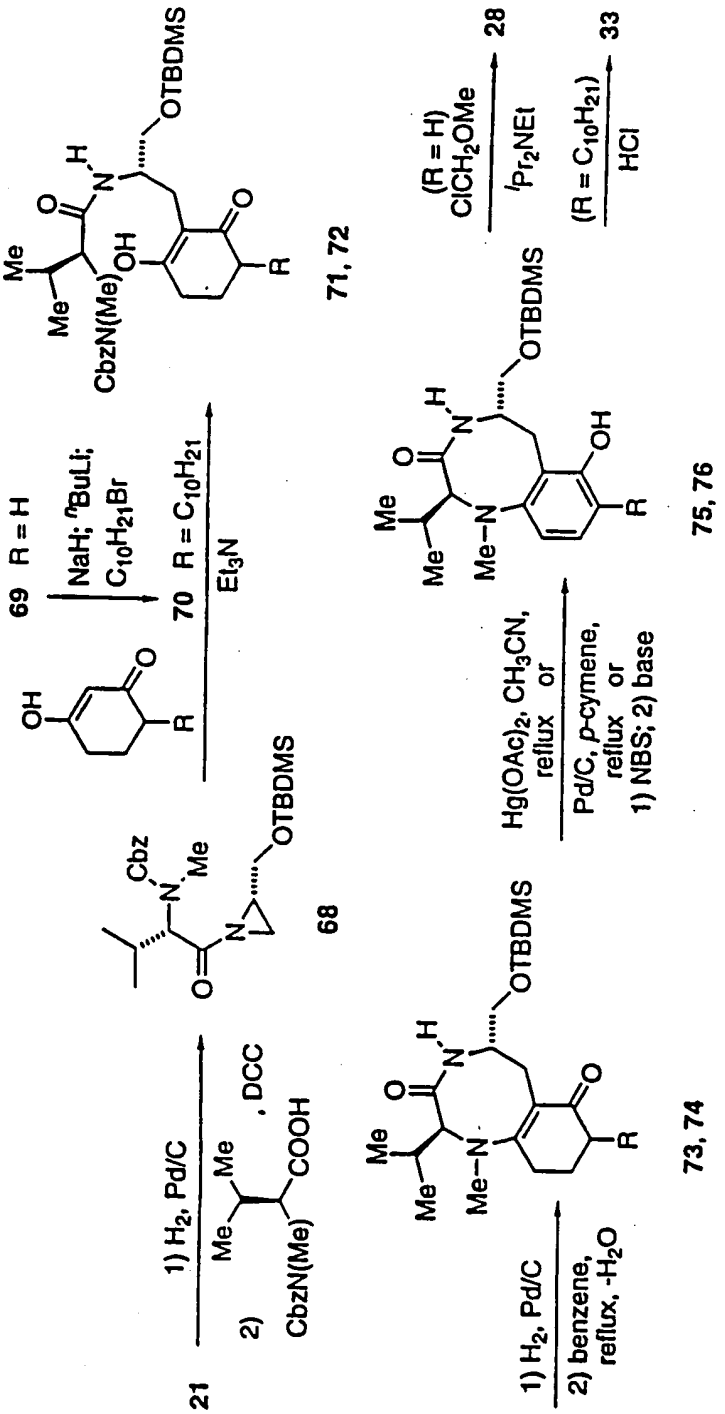

1) H2, Pd/C
2) CbzN(Me)CHMeCMe2COOH, DCC
21
68
69 R = H
NaH; nBuLi; C10H21Br
70 R = C10H21
Et3N
71, 72
1) H2, Pd/C
2) benzene, reflux, -H2O
73, 74
Hg(OAc)2, CH3CN, reflux or
Pd/C, p-cymene, reflux or
1) NBS; 2) base
75, 76
(R = H) ClCH2OMe
iPr2NEt
28
(R = C10H21)
HCl
33
OTBDMS
CbzN(Me)
Me
Cbz
Me-N
OH
O
R

FIG. 10

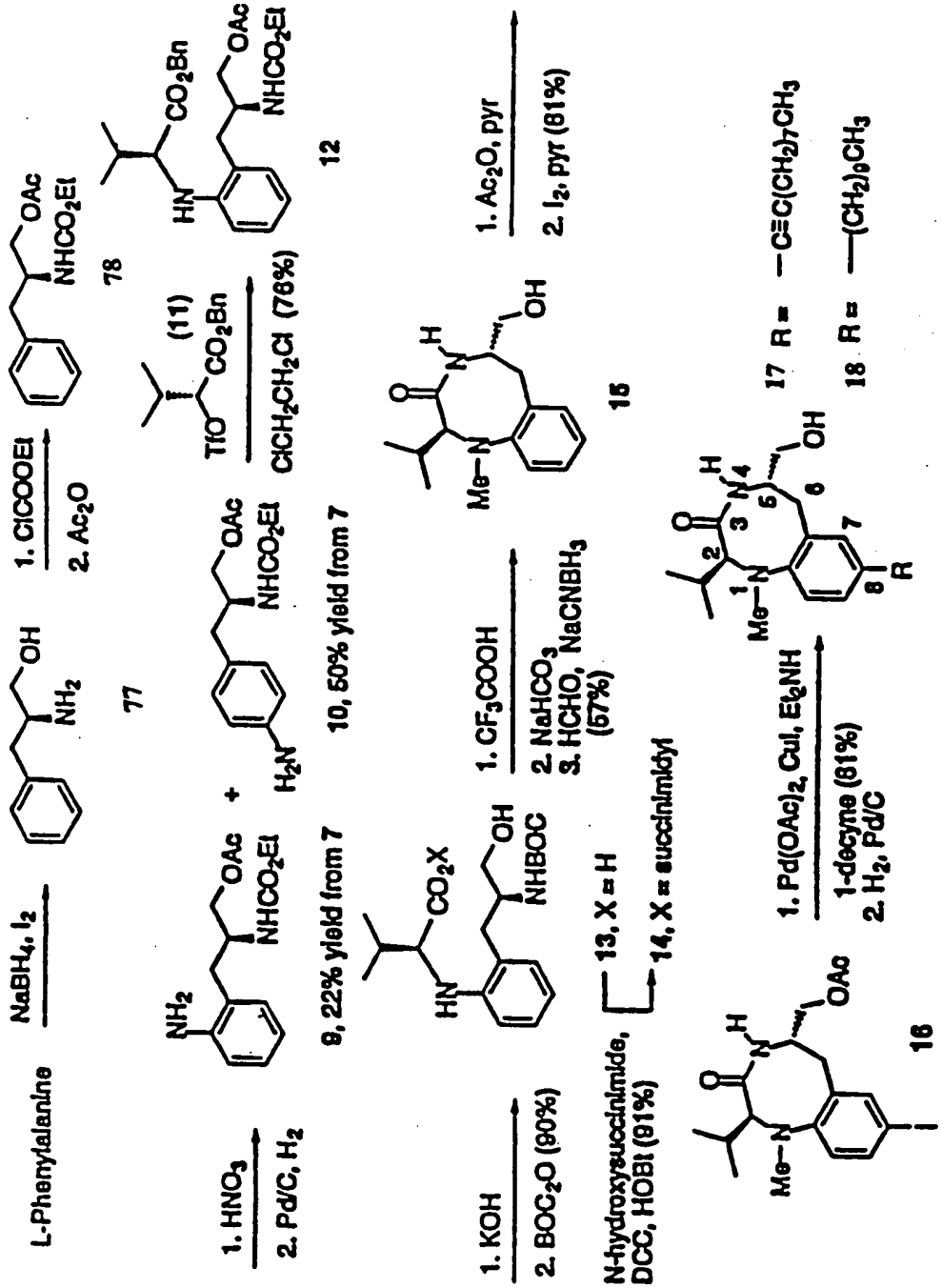

L-Phenylalanine
NaBH4, I2
77
1. ClCOOEt
2. Ac2O
78
(11)
ClCH2CH2Cl (76%)
12
1. HNO3
2. Pd/C, H2
8, 22% yield from 7
10, 50% yield from 7
1. KOH
2. BOC2O (90%)
1. CF3COOH
2. NaHCO3
3. HCHO, NaCNBH3
(57%)
15
1. Ac2O, pyr
2. I2, pyr (81%)
N-hydroxysuccinimide,
DCC, HOBt (91%)
13, X = H
14, X = succinimidyl
16
1. Pd(OAc)2, CuI, Et2NH
1-decyne (81%)
2. H2, Pd/C
17 R = —C≡C(CH2)7CH3
18 R = —(CH2)9CH3

FIG. 11

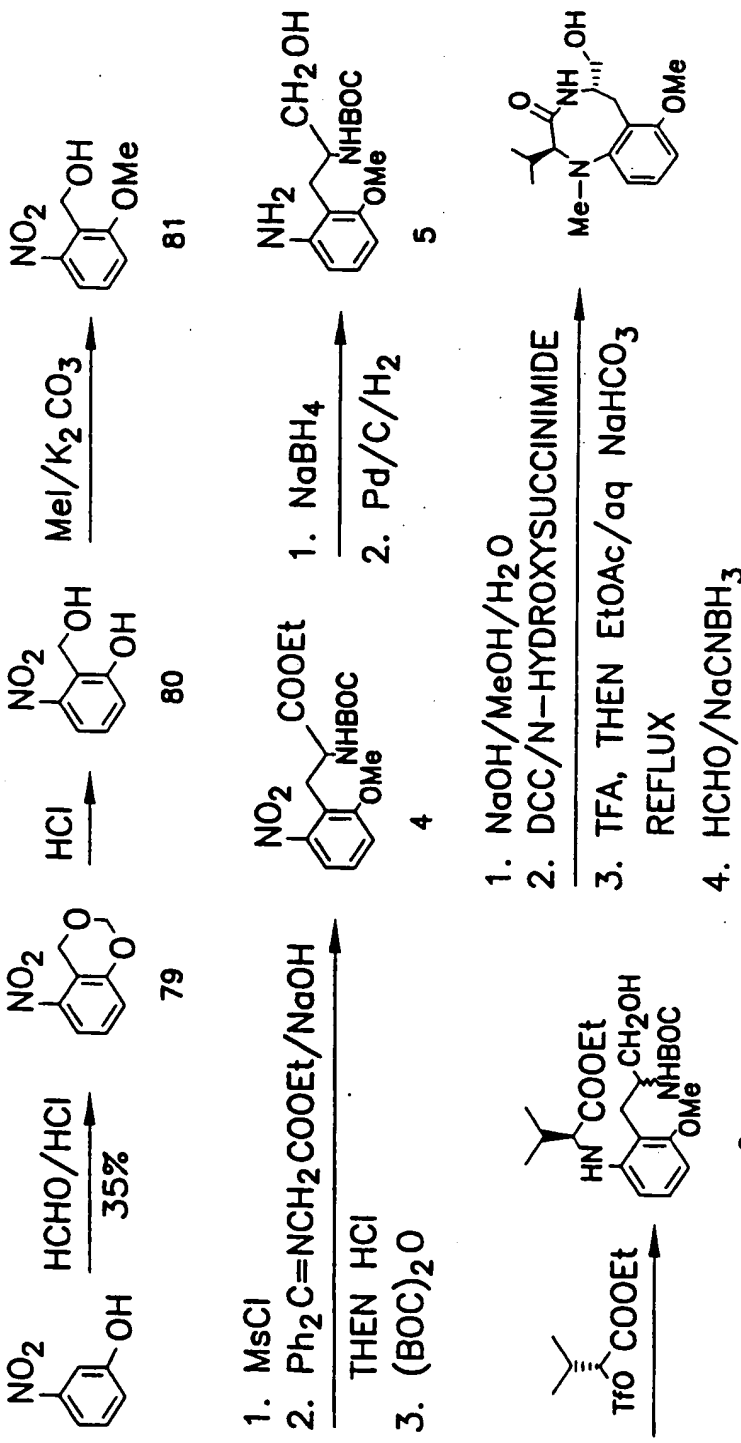

HCHO/HCl
35%
HCl
MeI/K2CO3
1. MsCl
2. Ph2C=NCH2COOEt/NaOH
THEN HCl
3. (BOC)2O
1. NaBH4
2. Pd/C/H2
1. NaOH/MeOH/H2O
2. DCC/N-HYDROXYSUCCINIMIDE
3. TFA, THEN EtOAc/aq NaHCO3
REFLUX
4. HCHO/NaCNBH3
1. I2/HgCl2
2. Pd/CuI/Decyne
R=
79
80
81
4
5
6
7
8

FIG. 12

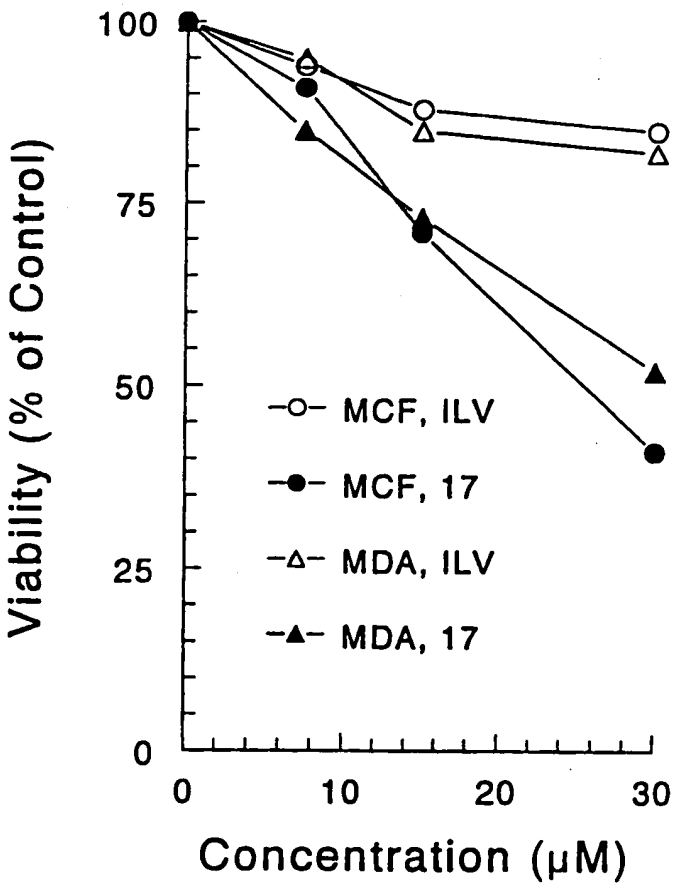

100
75
50
25
0
Viability (% of Control)
0
10
20
30
Concentration (μM)
MCF, ILV
MCF, 17
MDA, ILV
MDA, 17

FIG. 13

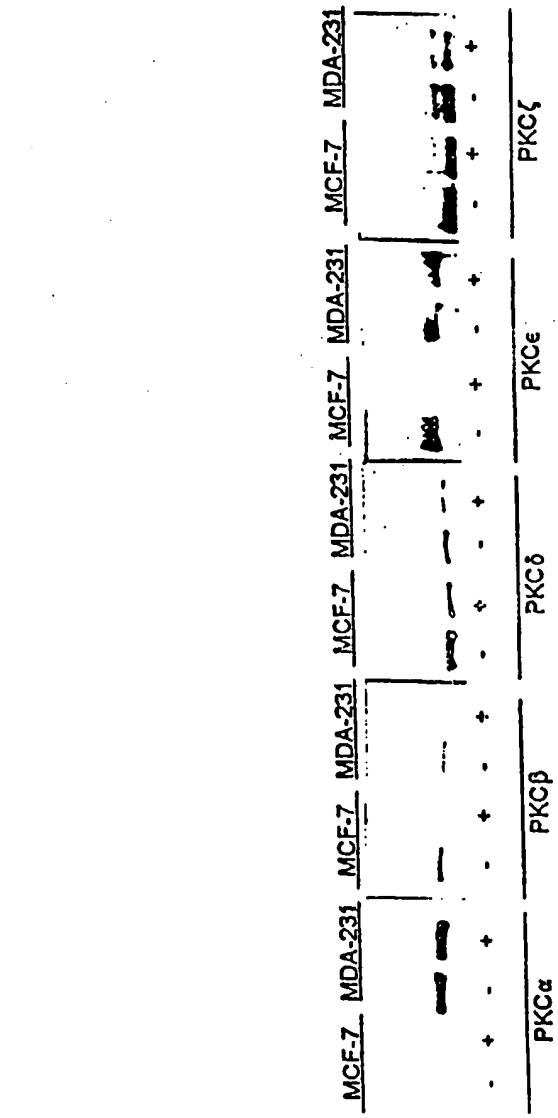

MCF-7
MDA-231
MCF-7
MDA-231
MCF-7
MDA-231
MCF-7
MDA-231
PKCα
PKCβ
PKCδ
PKCε
PKCζ

FIG. 14

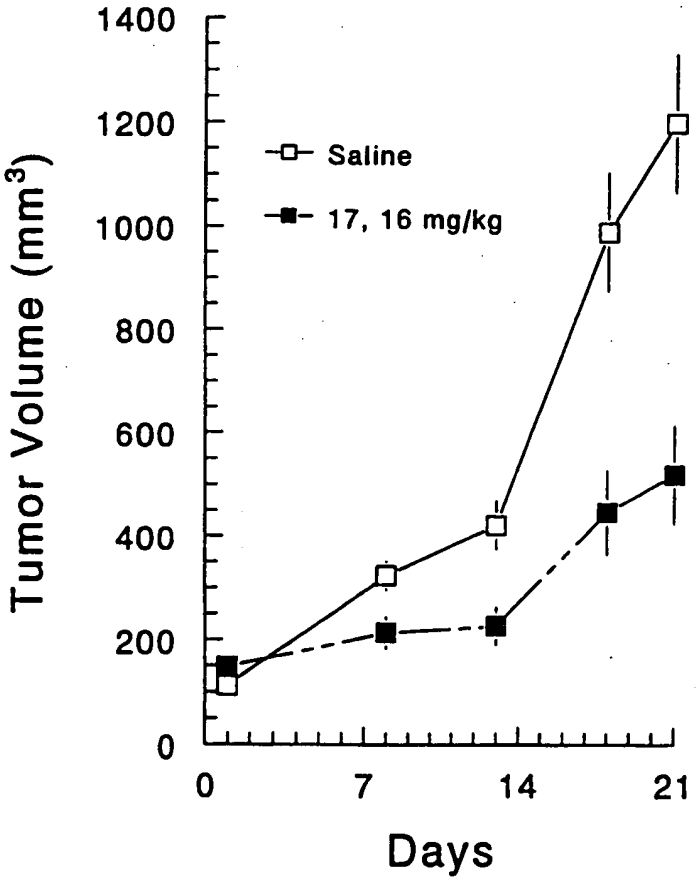

1400
1200
1000
800
600
400
200
0
Tumor Volume (mm3)
Saline
17, 16 mg/kg
0
7
14
21
Days

FIG. 15

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/08141

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D245/06 A61K31/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 09160 A (SHIONOGI & CO., LTD.) 6 April 1995 cited in the application see claims 1-4 & EP 0 721 945 A (...) 17 July 1996 ---	1,3,6,7, 9,10,13
P,X	WO 96 40614 A (PROCYON PHARMACEUTICALS, INC.;USA) 19 December 1996 see compounds P7BL, page 45 see claim 3 --- -/--	1-3,6,7, 9,10,13, 15,20

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 September 1997	'2 6. 09. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Hartramdf. G

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/08141

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	CHEMICAL & PHARMACEUTICAL BULLETIN (JAPAN), vol. 45, no. 2, February 1997, pages 424-426, XP002039501 ENDO Y. ET AL.: "Role of the hydrophobic moiety of tumor promoters. Synthesis and activity of benzolactams with alkyl substituents at various positions " cited in the application see compound 6, page 425	1,6,7,9, 10,13, 15,18,20
P,X	CHEMICAL & PHARMACEUTICAL BULLETIN (JAPAN), vol. 45, no. 3, March 1997, pages 573-575, XP002039502 ITAI A. ET AL.: "Advanced computational docking of two teleocidin congeners to cys2 domain of protein kinase C.delta." see compound 4c, page 573	1,6,7,9, 10,13, 15,18,20
P,X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 40, no. 9, April 1997, pages 1316-1326, XP002039503 KOZIKOWSKI A.P. ET AL.: "Modeling, chemistry, and biology of the benzolactam analogs of indolactam V (ILV). 2. Identification of the binding site of the benzolactams in the CRD2 activator-binding domain of PKC.delta. and discovery of an ILV analog of improved isoenzyme selectivity" see compounds 5 and 6, page 1317	1-3,6,7, 9,10, 13-15, 17,20
A	CHEMICAL & PHARMACEUTICAL BULLETIN (JAPAN), vol. 44, no. 5, May 1996, pages 1138-1140, XP002039504 ENDO Y. ET AL.: "Role of the hydrophobic moiety of tumor promoters. Synthesis and activity of 9-alkylated benzolactams"	1-20
A	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 118, no. 8, 28 February 1996, pages 1841-1855, XP002039505 ENDO Y. ET AL.: "Synthesis, conformation, and biological activity of teleocidin mimics, benzolactams. A clarification of the conformational flexibility problem in structure-activity studies of teleocidins" cited in the application see compounds 3, 6 and 14 see figures 4,5	1-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/08141

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 21 - 23
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 21 to 23 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compounds/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 97/08141

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9509160 A	06-04-95	CA 2173131 A	06-04-95
		EP 0721945 A	17-07-96
		US 5652232 A	29-07-97
WO 9640614 A	19-12-96	NONE	